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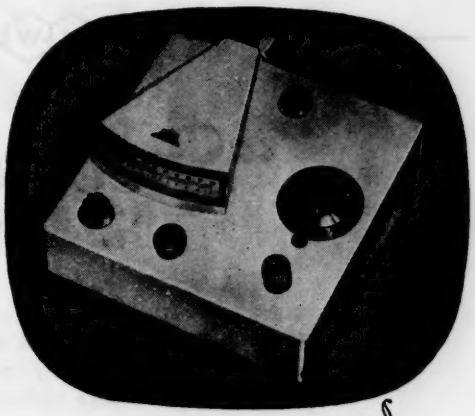

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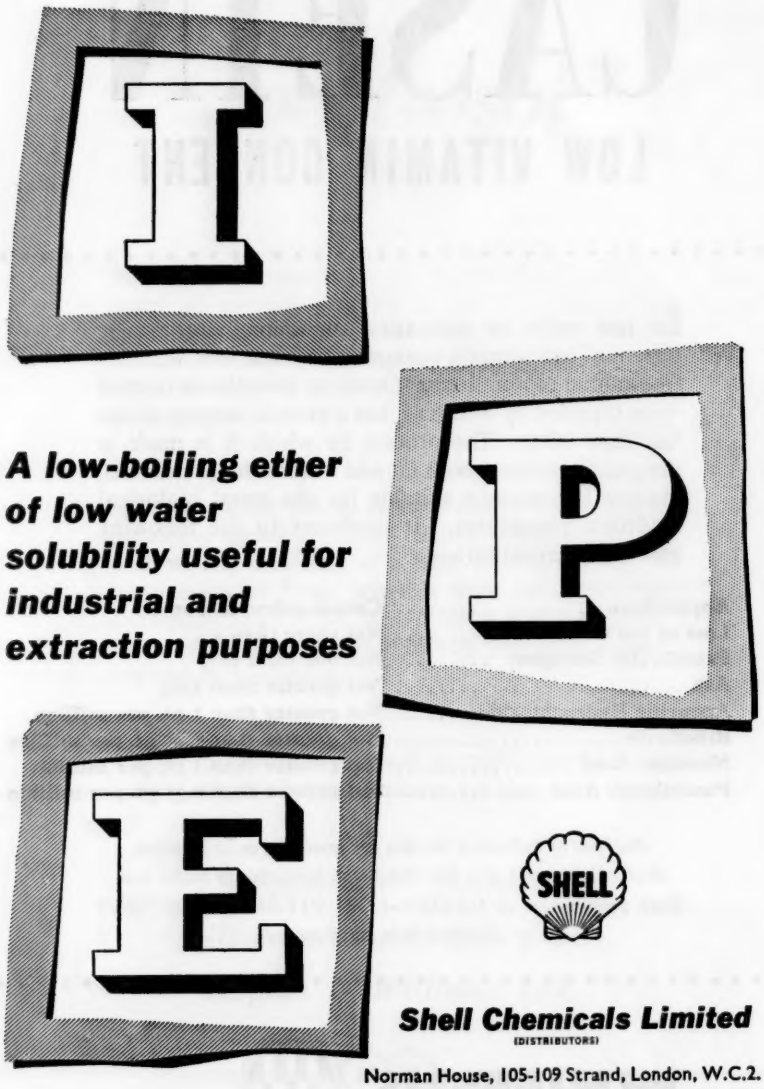

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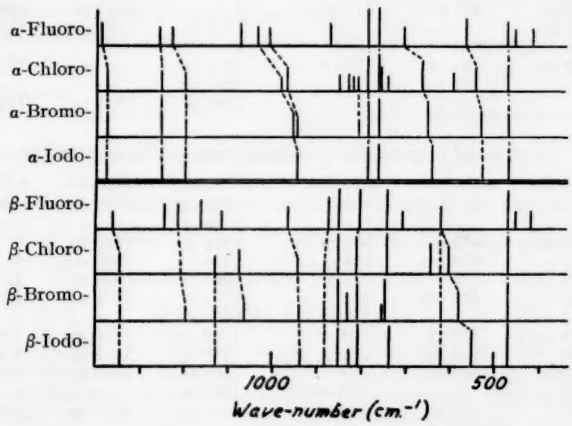
The Infra-red Spectra of the Monohalogenonaphthalenes.

By J. Ferguson and R. L. Werner.

[Reprint Order No. 5127.]

Recent work on the ultra-violet absorption and phosphorescence of monohalogenonaphthalenes has necessitated a knowledge of their vibration frequencies. To this end the infra-red spectra have been examined in *cyclo*hexane and also as pure liquids and solids. Certain relations have been suggested, and two frequencies discussed in relation to ultra-violet absorption.

In view of work on the absorption spectra (Ferguson, *J.*, 1954, 304) and the phosphorescence (Ferguson, Iredale, and Taylor, *J.*, 1954, 3160) of monohalogenonaphthalenes, it is necessary to obtain information about their vibration frequencies. Raman spectra have been published for α-fluoro- and β-bromo- (Goekel, *Z. physikal. Chem.*, 1935, *B*, **29**, 79; Luther, *Z. Elektrochem.*, 1948, **52**, 210), α- and β-chloro- (Goekel, *loc. cit.*; Luther, *loc. cit.*; Ziemecki, *Z. Physik*, 1932, **78**, 123), and α-bromo-naphthalene (Goekel, *loc. cit.*; Luther, *loc. cit.*; Ziemecki, *loc. cit.*; Dadieu and Kohlrausch, *Monatsh.*, 1931, **57**, 488).



Specific infra-red data for monohalogenonaphthalenes are lacking, although they have been included in a general presentation of the infra-red frequencies of substituted naphthalenes by Lecomte (*Compt. rend.*, 1939, **208**, 1636). In order to fill this deficiency we have examined their spectra in the region 400—1400 cm.$^{-1}$ in *cyclo*hexane solution, the α-series also as pure liquids and the β-series as solids. The frequencies found are contained in Tables 1—4. A detailed discussion of them and of their relation to the naphthalene fundamentals is not possible. We have therefore included a line diagram of the frequencies found, and shown possible relations by means of broken lines. These trends, although tentative, help to show major differences between the α- and the β-series.

A most interesting feature of their spectra is the appearance of the fundamental 470 cm.$^{-1}$ in both series. It is unaltered both by type of substituent and position in the ring. This vibration is the counterpart of the controversial 473 vibration of naphthalene. Its probable appearance in the absorption spectra of these compounds has been discussed (Ferguson, *loc. cit.*).

Luther (*loc. cit.*) has derived an empirical equation for determining the value of the naphthalene 764 a_g fundamental (ω_4 in Luther's notation) in the α-substituted derivatives. We find that this Raman-active vibration is also strongly infra-red active, recording the good coincidences shown in Table 5.

TABLE 1. *Infra-red frequencies of α-halogenonaphthalenes in* cyclo*hexane.*

α-Fluoro-	α-Chloro-	α-Bromo-	α-Iodo-	α-Fluoro-	α-Chloro-	α-Bromo-	α-Iodo-
414 m	—	—	—	—	808 m	807 m	—
456 m	—	—	—		821 m	—	—
473 ms	471 ms	470 m	471 m	—	830 m	—	—
567 s	541 ms	532 ms	525 m	—	852 m	—	—
—	595 m	—	—	874 ms			
709 m	663 ms	650 s	642 s	1011 m	969 ms	948 m	
—	740 m	—	—	1036 m	984 m	956 ms	944 ms
—	758 ms	—	—	1074 ms	—	—	—
764 vs	764 vs	763 vs	762 vs	1229 m	1201 m	1197 m	1199 m
791 vs	789 vs	788 vs	787 vs	1258 m	1252 m	1253 ms	1253 m
				1391 m	1375 m	1376 ms	1380 m

In all Tables, w = weak, mw = medium to weak, m = medium, ms = medium to strong, s = strong, vs = very strong.

TABLE 2. *Infra-red frequencies of β-halogenonaphthalenes in* cyclo*hexane.*

β-Fluoro-	β-Chloro-	β-Bromo-	β-Iodo-	β-Fluoro-	β-Chloro-	β-Bromo-	β-Iodo-
418 m	—	—	—	804 vs	808 vs	807 vs	807 vs
454 m	—	—	—	—	—	832 s	824 m
471 s	471 s	470 vs	469 s	851 vs	851 vs	851 vs	851 vs
—	—	—	548 ms	871 ms	879 m	882 m	881 m
—	603 ms	581 s	—	963 m	941 m	939 m	934 m
620 ms	622 m	620 m	617 mw	—	1075 m	1063 m	—
—	641 ms	—	—	1112 m	1128 m	1130 m	1128 m
707 m	—	—	—	1160 ms	—	—	—
738 vs	740 vs	741 vs	737 vs	1214 ms	—	1192 m	—
—	—	757 m	—	1246 ms	—	—	—
				1360 m	1345 m	1344 m	1342 m

TABLE 3. *Infra-red frequencies of α-halogenonaphthalenes in the liquid state.*

α-Fluoro-	α-Chloro-	α-Bromo-	α-Iodo-	α-Fluoro-	α-Chloro-	α-Bromo-	α-Iodo-
415 m	—	—	—	1011 m	983 w	956 ms	967 w
455 m	—	—	—	1035 m	—	—	1020 m
473 m	472 m	471 m	472 m	1074 ms	1143 m	—	1128 m
567 s	541 s	532 ms	524 ms	1229 s	1200 ms	1199 m	1199 ms
—	494 m	—	—	1260 s	1251 m	1251 m	1251 s
709 ms	663 s	649 ms	642 s	1390 s	1378 s	1376 s	1376 s
—	743 m	—	730 m	1456 m	—	—	—
764 vs	764 vs	762 vs	763 vs	1508 ms	1500 ms	1500 m	1495 s
792 vs	791 vs	788 vs	787 vs	1576 ms	1562 m	1560 m	1555 ms
—	829 m	805 m	—	1600 ms	1589 m	1602 m	1590 m
874 m	851 m	—	856 m	1640 w	—	—	—
—	967 s	946 m	942 s	3080 m	3075 m	3080 m	3072 m

TABLE 4. *Infra-red frequencies of β-halogenonaphthalenes in Nujol mull.*

β-Fluoro-	β-Chloro-	β-Bromo-	β-Iodo-	β-Fluoro-	β-Chloro-	β-Bromo-	β-Iodo-
418 m	—	—	—	879 s	888 ms	887 m	—
453 m	—	—	—	896 m	—	—	896 m
470 ms	470 s	475 vs	475 vs	—	940 m	939 m	932 ms
		580 mw	567 mw	—	—	—	947 m
—	602 ms	—	—	960 ms	962 m	—	961 m
618 m	625 m	619 m	—	—	1074 ms	1063 ms	1056 w
—	639 m	—	—	1156 m	1127 m	1130 m	1126 m
662 m	—	—	—	1212 ms	—	—	—
706 s	—	—	—	1247 ms	—	—	—
749 vs	746 vs	743 vs	735 vs	1357 ms	1343 m	1343 m	1338 m
—	787 m	789 m	765 m	1438 m	—	1377 ms	—
813 vs	817 vs	812 vs	815 vs	1510 s	1500 m	1500 m	1496 m
—	—	832 ms	—	1578 s	1572 m	1587 ms	—
—	851 m	851 ms	—	1602 ms	—	—	1610 ms
858 s	861 s	860 ms	865 ms	1630 m	—	—	—

TABLE 5.

α-X	ω_4 Raman (Luther)	ω_4 infra-red	α-X	ω_4 Raman (Luther)	ω_4 infra-red
F	709	709	Br	651	650
Cl	665	663	I	—	642

McConnell and McClure (*J. Chem. Phys.*, 1953, **21**, 1296) have assigned the naphthalene a_g 512 fundamental the value 430 cm.$^{-1}$ in the first excited singlet state. However, work on the absorption spectra of the halogenonaphthalenes has revealed a frequency of the value about 470 cm.$^{-1}$ in the first excited singlet level of these compounds. Examination of the infra-red and Raman data shows only two vibrations, in this region, that do not change appreciably with substitution, *viz.*, the 473 and 512 of naphthalene. The 473 mode is non-totally symmetric in naphthalene and is not expected to appear strongly as a progression in the spectra of the halogenonaphthalenes. Furthermore, it should be lowered in value in the excited state, so that identification with the observed frequency is not very likely. The frequency, however, is satisfactorily explained in terms of the 512 mode of naphthalene and the evidence for the assignment of this vibration to the value 430 cm.$^{-1}$ in the excited state must be considered very weak.

Experimental

The infra-red spectra were obtained with a Perkin-Elmer 12C spectrometer with a 13-cycle amplifier, sodium chloride and potassium bromide prisms being used. Calibration was effected in the normal manner, bands of water vapour, ammonia, and carbon dioxide being used for the sodium chloride region, and methanol vapour for the potassium bromide region.

Solids were examined as Nujol mulls, and pure liquids as capillaries between plates. The *cyclo*hexane solutions were 20% w/v, a 0·050-mm. cell being used for the sodium chloride region and a 0·20-mm. cell for the potassium bromide region.

The purity of the compounds has been reported elsewhere (Ferguson, *loc. cit.*; Ferguson, Iredale, and Taylor, *loc. cit.*).

University of Sydney.
N.S.W. University of Technology, Australia. [*Received, February 16th*, 1954.]

Reactions of Dialkyl Phosphorobromidates relating to the Reaction of Phosphoryl Bromide with Alcohols and with Trialkyl Phosphates.

By W. Gerrard and G. J. Jeacocke.

[Reprint Order No. 5253.]

Tributyl phosphite and bromine quickly gave the alkyl bromide and dibutyl phosphorobromidate, which gave alkyl bromide slowly at 15°, quickly at 95°, and by hydrogen bromide was quickly dealkylated to alkyl bromide. Because of the last reaction the bromidate cannot be isolated when the hydrogen phosphite is used with bromine. With (+)-2-octyl compounds, (−)-2-bromo-octane was formed. Neither the dibromidate nor the bromidate (*n*-butyl) could be isolated by the reaction between phosphoryl bromide and the alcohol or trialkyl phosphate.

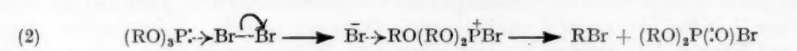
Compared with phosphoryl chloride–alcohol systems (Walczynska, *Roczn. Chem.* 1926, **6**, 110; Gerrard, *J.*, 1940, 1464; 1945, 106; Gerrard, Green, and Nutkins, *J.*, 1952, 4076), phosphoryl bromide systems differ markedly in the lower stability of the dialkyl phosphorobromidate, the quicker dealkylation of the esters by hydrogen bromide, and the greater ease of replacement of the third atom of halogen by alkoxyl in the presence of a tertiary base.

Dibutyl phosphorobromidate, prepared by the reaction (1), gave an almost quantitative yield of 1-bromobutane at 15° (several days) and at 95° (15 min.). The phosphite from

(1) $$P(OR)_3 + Br_2 \longrightarrow RBr + (RO)_2P(:O)Br$$

(+)-octan-2-ol gave (−)-2-bromo-octane by the primary reaction with bromine, and the accompanying bromidate gave also the (−)-halide when heated, there being an inversion of configuration, with little loss in optical activity, in both reactions. Addition of bromine to the phosphite, resulting in the compound $(RO)_3PBr_2$, followed by an intramolecular

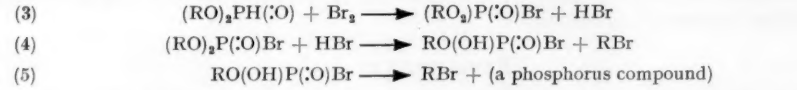
elimination of alkyl bromide would lead to retention of configuration. The mechanism suggested is therefore (2) (cf. Gerrard and Philip, *Research*, 1948, **1**, 477):



(2)

Decomposition of the bromidate could hardly have been intramolecular either, and probably involved a bromide ion formed by a mechanism not yet clear.

From the bromidate, hydrogen bromide readily removed both alkyl groups as alkyl bromide, and because of this the bromidate cannot be isolated by the interaction of bromine and butyl hydrogen phosphite (3); reaction (4) occurs, followed by (5):



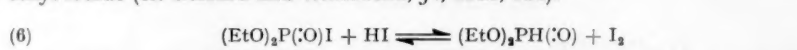
(3)

(4)

(5)

By reactions (3) and (4) di-2-octyl (di-1-methyl-*n*-heptyl) hydrogen phosphite [from (+)-octan-2-ol] gave (−)-2-bromo-octane probably without loss in rotatory power, but there was some loss by reaction (5).

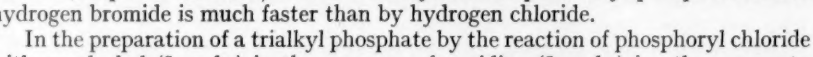
McCombie, Saunders, and Stacey (*J.*, 1945, 380) recommended the hydrogen phosphite instead of the trialkyl phosphite for the preparation of a phosphorochloridate. There is no choice with bromine—the triester must be used. Neither is there a choice with iodine, as McCombie, Saunders, and Stacey (*J.*, 1945, 921) found; and although they attributed lack of success with the hydrogen phosphite to the reduction of diethyl phosphoroiodidate by hydrogen iodide they were aware that the reaction was more complicated than is represented by equation (6). It appears that the dominating process here is dealkylation to ethyl iodide (cf. Gerrard and Whitbread, *J.*, 1952, 914).



(6)

Attempts to prepare butyl phosphoro-dibromidate and -bromidate by the interaction of tributyl phosphate and phosphoryl bromide were fruitless. Little definite except alkyl bromide could be obtained by the reaction between butan-1-ol (3 mols.) and phosphoryl bromide (1 mol.); but with the latter in equimolecular proportion, the residue, after removal (below 20°) of volatile matter including any unchanged oxybromide, appeared to contain dibromidate as judged from the bromine content. We were unable to study the dealkylation of the dibromidate by hydrogen bromide, but there is evidence (Gerrard and Nutkins, unpublished work) that the dealkylation of pure butyl phosphorodichloridate by hydrogen bromide is much faster than by hydrogen chloride.

In the preparation of a trialkyl phosphate by the reaction of phosphoryl chloride (1 mol.) with an alcohol (3 mols.) in the presence of pyridine (3 mols.) in ether or pentane, base hydrochloride equivalent to 2 atoms of chlorine is quickly formed (cf. Gerrard and Shepherd, *J.*, 1953, 2069), but the third equivalent is only slowly precipitated at 15°, as is clearly



(7)

shown by using the chloridate (7). On a steam-bath precipitation is complete in 5 hr. With phosphoryl bromide, however, complete precipitation of hydrobromide was quickly achieved at 15°, and so this reagent is useful for the preparation of trialkyl phosphates at room temperature.

Experimental

Formation of Dibutyl Phosphorobromidate.—Into tributyl phosphite (41 g.), bromine, in carbon dioxide as carrier gas, was passed until the liquid became red, 26·3 g. being absorbed. At 15°/15 mm. 1-bromobutane (22·4 g.) was removed and trapped at −80°. The yield corresponds with the equation: $(RO)_3P + Br_2 \longrightarrow O{:}PBr(OR)_2 + RBr$. The residue (44·8 g.) appeared to be a good specimen of *dibutyl phosphorobromidate* (Found: Br, 29·25; P, 11·4. $C_8H_{18}O_3BrP$ requires Br, 29·3; P, 11·35%). Hydrolysis was conducted in aqueous sodium

hydroxide to determine halogen. The bromidate (15·1 g.) decomposed when an attempt was made to distil it at 0·001 mm., and 1-bromobutane (8·1 g.), b. p. 100—101°, was collected in the cold trap; this weight corresponds to the complete removal of all the bromine and one alkyl group. From the bromidate (8·5 g.), after it had been heated on a steam-bath for 15 min., 1-bromobutane (4·0 g.), b. p. 101°, d_4^{25} 1·2684, containing all the bromine originally present, was obtained.

When air was used instead of carbon dioxide as carrier gas, some of the phosphite was oxidised to phosphate.

The bromidate (3·41 g.) was allowed to remain at room temperature for several days, and then 1-bromobutane (1·68 g., 98%), b. p. 101°, d^{25} 1·2684 (Found: Br, 58·3. Calc. for C_4H_9Br: Br, 58·4%), was isolated at 15°/15 mm.

Dealkylation of Dibutyl Phosphorobromidate.—Dry hydrogen bromide was passed into the bromidate (17·1 g.) at −5° for 1 hr., by which time 10·2 g. of the gas had been absorbed. At 15°/15 mm. 1-bromobutane (16·8 g., 98% for 2 alkyl groups), b. p. 101°, d_4^{25} 1·2684, was isolated. Some alkyl bromide was formed when the bromidate was poured on ice or into water, and we ascribe this to dealkylation by hydrogen bromide before it can be dispersed in the water. For this reason it is necessary to hydrolyse the bromidate with aqueous alkali.

Interaction of Bromine and Dibutyl Hydrogen Phosphite.—Bromine vapour in a stream of carbon dioxide was passed into the hydrogen phosphite (6·1 g.) at −5°, but colour appeared immediately, and it was only when the flask was removed from the cooling bath that decoloration quickly occurred. More bromine was admitted at −5°, with the same result. By repeating the operation permanent coloration showing excess of bromine was obtained. Increase in weight was 5·0 g., equiv. to 1 mol. of bromine per mol. of hydrogen phosphite. At 15°/15 mm. 1-bromobutane (4·3 g.), b. p. 101° (Found: Br, 58·2%), was isolated from a residue (6·8 g.) which by hydrolysis with cold alkali was shown to be equivalent to O:PBr(OH)OR (Found: Br, 36·8%; equiv., 72·0. $C_4H_{10}O_3BrP$ requires Br, 36·9%; equiv., 72·3). This *butyl hydrogen phosphorobromidate* (6·1 g.), after being at −30° for 40 hr., gave at 15°/15 mm. 1-bromobutane (3·7 g.) which accounts for 96% of the bromine present.

Interaction of Di-n-butyl Phosphorobromidate and Phosphoryl Bromide.—Phosphoryl bromide (10·8 g., 1 mol.) was mixed with bromidate (9·1 g., 1 mol.). After 4 weeks at 15° only 0·20 mol. of phosphoryl bromide had reacted; but 1·18 mols. of 1-bromobutane had been formed. After 7 weeks the numbers were 0·22 and 1·31, and after 19 weeks 0·23 and 1·44. It therefore appeared that alkyl bromide was formed partly, at least, independently of reaction concerning the oxybromide.

Interaction of Tributyl Phosphate and Phosphoryl Bromide.—Preliminary experiments showed that interaction was slow, and that 1-bromobutane was formed, and an additional amount was formed when the reaction mixture was poured on ice with the purpose of isolating the acid esters. Hydrolysis with sodium hydroxide solution avoided this source of alkyl bromide, and it was shown that in these conditions the already formed alkyl bromide was not affected. Two examples are given of the results when hydrolysis was by ice.

The phosphate (25·7 g., 2 mol.) and phosphoryl bromide (13·55 g., 1 mol.) were mixed, and 3 aliquot portions of the mixture were kept at 15° for respectively 9, 18, and 29 days. The yields of 1-bromobutane (in mols.) were: 2·25, 2·32, and 2·84. The corresponding yields for a different proportion of reagents (phosphate, 12·8 g., 1 mol.; phosphoryl bromide, 27·5 g., 2 mol.) were 1·63, 1·66, and 1·74.

In the following procedure, treatment with water was avoided. After the stated interval, alkyl bromide was isolated at 20°/15 mm. (trap at −80°), and then unchanged phosphoryl bromide was obtained at 20°/0·1 mm. (trap at −80°).

Mol. ratio $(RO)_3PO$: $POBr_3$	2 : 1		1 : 1		0·5 : 1	
RBr and $POBr_3$ (mols.) reacting at 20° in x days:	RBr	$POBr_3$	RBr	$POBr_3$	RBr	$POBr_3$
$x = 3$	0·32	0·32	0·28	0·48	0·25	0·48
6	—	—	—	—	0·48	0·92
9	1·05	0·86	0·89	0·92	0·79	0·96
14	1·52	0·87	1·20	0·96	0·89	0·98
19	1·96	0·88	1·40	0·99	—	—

The specimens of 1-bromobutane were obtained in good purity, *e.g.*, b. p. 100—101°, n_D^{13} 1·443, d_4^{25} 1·2680 (Found: Br, 58·2. Calc. for C_4H_9Br: Br, 58·4%).

Interaction of Phosphoryl Halides and Alcohols in the Presence of Pyridine.—Gerrard and Stranz (unpublished work) found that, when butan-1-ol, pyridine, and phosphoryl chloride are

mixed in ethereal solution the replacement of the first chlorine atom by alkoxyl is quick at 15°, replacement of the second is slower, and of the third is very much slower. Thus with the reagents in the ratio $POCl_3$: ROH : C_5H_5N = 1 : 1 : 1 at a concentration of 0·5 mole/l. with respect to oxychloride, base hydrochloride was almost quantitatively (98%) formed in 6 min., whereas with the ratio 1 : 2 : 2 50% of the total chlorine was replaced in 6 min., and 55% in 1 hr., and with the ratio 1 : 3 : 3 70% of the total was replaced in 6 min., 84% in 12 hr., and 92% in 24 hr. Similarly with the dichloridate (1 mol.), alcohol (2 mol.), and base (2 mol.), 36% of the chlorine was replaced in 6 min., 63% in 2 hr., and 80% in 12 hr.; and with the chloridate (1 mol.), alcohol (1 mol.), and base (1 mol.) 3% of the chlorine was replaced in 6 min., 16% in 1 hr., and 90% in 24 hr.

We now show that for the ratio ROH : $POCl_3$: C_5H_5N = 3 : 1 : 3, at the same concentration in pentane the chlorine replaced was as follows: at −30°, 0·1 hr. (55%); at 35°, 2·5 hr. (86%); and at 35°, 5 hr. (99%). For *iso*butyl alcohol at 35°, the value after 5 hr. was 98%. When the oxybromide was used in place of the oxychloride with both these alcohols 98% of the bromine was replaced in 0·3 hr. at −30°.

The precipitates were good specimens of the hydrohalide (*e.g.*, Found: Cl, 30·7; C_5H_5N, 68·3. Calc. for C_5H_6NCl: Cl, 30·75; C_5H_5N, 68·4. Found: Br, 49·5; C_5H_5N, 50·1. Calc. for C_5H_6NBr: Br, 50·0; C_5H_5N, 49·4%). From reaction with the oxybromide at −30°, and from reaction with the oxychloride at 35° (5 hr.), tributyl phosphate, b. p. 116—118°/0·1 mm. (Found: P, 11·6. Calc. for $C_{12}H_{27}O_4P$: P, 11·65%), and tri*iso*butyl phosphate, b. p. 116—118°/0·1 mm. (Found: P, 11·6%), were obtained.

Iodine and Triethyl Phosphite or Hydrogen Phosphite.—Iodine (2·54 g., 0·01 mole) and triethyl phosphite (1·67 g., 0·01 mole) were mixed in pentane (McCombie *et al.*, *J.*, 1945, 921, used ether) at 0°. Removal of the solvent at low pressure (trap at −78°) gave two layers, and from the upper one, together with trap contents, ethyl iodide (2·36 g., 50% based on *three* ethyl groups), b. p. 71·8° (Found: I, 81·8. Calc. for C_2H_5I; I, 81·4%), was obtained. When hydrogen iodide was passed into the reaction mixture before distillation, ethyl iodide (8·99 g., 96% based on three alkyl groups in the phosphite, 3·3 g.), b. p. 71·6° (Found: I, 81·3%), was obtained.

Iodine (2·54 g., 0·01 mole) in dry pentane (10 c.c.) was added slowly to diethyl hydrogen phosphite (1·36 g., 0·01 mole) at 0°. The iodine was slowly decolorised, more quickly at 15°, and when half of the iodine had been added a brown oil began to separate. After 12 hr. there was a brown lower layer and a colourless upper solution from which ethyl iodide (1·55 g., 50% based on 2 alkyl groups), b. p. 72° (Found: I, 81·5%), was obtained.

Reaction of Phosphoryl Bromide with Butan-1-ol.—The oxybromide (6·5 g., 1·04 mol.) and butan-1-ol (1·6 g., 1 mol.) were mixed in ether (12 c.c.) at 20°. After 2 hr., volatile matter was withdrawn at 20°/14 mm., leaving a residue (6·3 g.) which at 20°/0·1 mm. afforded 1-bromobutane (0·6 g.), b. p. 99—100°, n_D^{20} 1·4400, and a further residue (5·52 g.). At 100°/0·1 mm., the residue gave 1-bromobutane (1·45 g.), b. p. 100°, n_D^{20} 1·4400, and a residue (1·5 g.) (Found: Br, 25·0%). Phosphoryl bromide (1·65 g.) condensed as a white solid in the trap tubes. Therefore the amount which had reacted gave 2·05 g. of alkyl bromide (Calc.: 2·29 g.). With the oxybromide (2·1 g., 0·33 mol.) and alcohol (1 mol.), 1-bromobutane (1·0 g.), and a residue (1·8 g.) (Found: Br, easily hydrolysed, 10·2%) were obtained at 20°/0·1 mm. The residue decomposed on attempted distillation.

Experiments with Optically Active Substances.—The (+)-octan-2-ol (Kenyon, *J.*, 1922, 121, 2540) used had α_D^{20} +8·0° (l = 1). (All rotatory powers are for l = 1.) In ether, the alcohol (3 mol.), pyridine (3 mol.), and oxybromide (1 mol.) behaved as did butan-1-ol, quickly affording base hydrobromide (98%) (Found: Br, 49·9; C_5H_5N, 48·6%) and, from the washed and dried solution, a residue (no distillate up to 110°/15 mm.), α_D^{16} +6·9° (Found: P, 6·9. Calc. for $C_{24}H_{51}O_4P$: P, 7·1%). The aqueous washings contained no phosphate ions, and merely a trace of bromide ions. Octan-1-ol (6·5 g. 1 mol.) behaved precisely similarly; the residue weighed 6·35 g. (after being at 140°/15 mm.) (Found: P, 6·9%).

Tri-2-octyl (tri-1-methylheptyl) phosphite (Gerrard, *J.*, 1944, 85) (8·3 g., 1 mol.) was treated with bromine as described. The mixture was added to dilute aqueous sodium hydroxide, and from the dried ethereal extract 2-bromo-octane (3·8 g.), b. p. 67°/9 mm., n_D^{17} 1·4517, α_D^{17} −41·0° (Found: Br, 40·8. Calc. for $C_8H_{17}Br$: Br, 41·4%), was obtained. When the primary mixture was heated on a steam-bath for 0·5 hr. before treatment with alkali, 2-bromo-octane (5·9 g.), b. p. 67°/9 mm., n_D^{17} 1·4520, α_D^{17} −41·2° (Found: Br, 41·0%), was obtained.

Similarly from the hydrogen phosphite (10·0 g.) (Gerrard, *J.*, 1944, 85) and bromine, there was very little hydrogen bromide evolved, and after dry air had been passed for 30 min. the residue (15·95 g.) was divided into two parts, A (7·35 g.) and B (8·60 g.). Part A was added to

aqueous sodium carbonate, and from the dried ethereal extract 2-bromo-octane (2·0 g.), b. p. 72°/13 mm., n_D^{17} 1·4510, d_4^{20} 1·0982, α_D^{20} −40·1° (Found: Br, 41·4%), and octene (0·55 g.), trapped at −80° and giving dibromo-octane (0·8 g.), b. p. 109°/13 mm., n_D^{20} 1·4960, were obtained. On acidification, the carbonate solution gave an oil (2·2 g.) (Found: P, 11·65%). Part B was set aside for 96 hr. at 20°, and then treated as for part A. The distillate had a long boiling range, 66—90°/14 mm., α_D^{20} −33·4°, d_4^{15} 1·1198, n_D^{20} 1·4535, and after several fractionations 2-bromo-octane (3·17 g.), b. p. 77—80°/18 mm., α_D^{20} −38·00°, n_D^{20} 1·4518, was separated. When bromine (5·34 g.) was added dropwise to the hydrogen phosphite (10·0 g.) at 0°, no hydrogen bromide was evolved. Portion A gave similar results, and portion B (7·8 g.) was heated at 100° for 12 min. A solution of sodium carbonate gave with the product an oil (5·95 g.) comprising mainly 2-bromo-octane (4·47 g.), b. p. 74°/14 mm., α_D^{20} −36·6°, and dibromo-octane (1·25 g.), b. p. 109—114°/12 mm.

Materials.—Tributyl phosphite and dibutyl phosphite were prepared as described by Gerrard (*J.*, 1940, 1464). Phosphoryl bromide was obtained as a white crystalline substance by interaction of phosphorus pentabromide and *iso*propanol (Gerrard, Nechvatal, and Wyvill, *Chem. and Ind.*, 1947, 437).

We thank Mr. R. W. Madden for checking the results with (+)octan-2-ol. We gratefully acknowledge a grant from the Research Fund of the Chemical Society.

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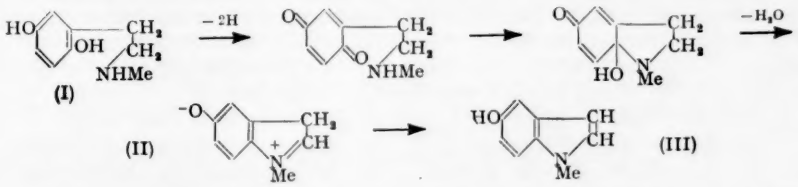
Hydroxytryptamines. Part II. A New Synthesis of Physostigmine.*

By JOHN HARLEY-MASON and A. H. JACKSON.

[Reprint Order No. 5290.]

(±)-Eseroline has been synthesised by ferricyanide oxidation of 2-(2 : 5-dihydroxyphenyl)-2 : *N* : *N'*-trimethylbutane-1 : 4-diamine and converted into (±)-eserethole. Similar oxidation of 2-(2 : 5-dihydroxyphenyl)-*N*-methylethylamine gives 5-hydroxy-1-methylindole.

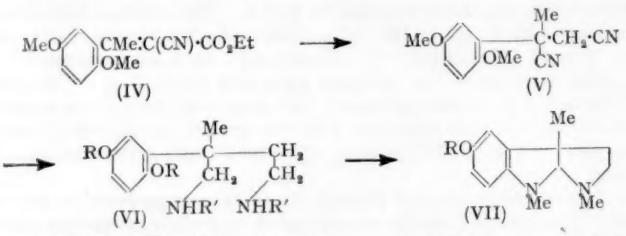
IN Part I * it was shown that ferricyanide oxidation of 2-(2 : 5-dihydroxyphenyl)butane-1 : 4-diamine gave 5-hydroxytryptamine (serotonin) in good yield. Eseroline (VII; R = H), the hydrolysis product of physostigmine (eserine), may be regarded as a trimethyl-5-hydroxytryptamine in which a second ring-closure has occurred, and we therefore investigated the oxidation of the appropriate trimethylbutanediamine. To determine the effect of *N*-methylation on the formation of 5-hydroxyindoles from 2 : 5-dihydroxyphenylethylamines a model experiment was first conducted. 2-(2 : 5-Dimethoxyphenyl)ethylamine with benzaldehyde gave a Schiff base which after being



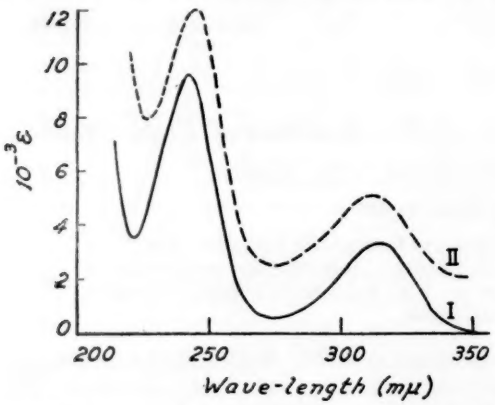
heated with methyl iodide and subsequent hydrolysis gave the monomethyl derivative. This with boiling hydrobromic acid gave 2-(2 : 5-dihydroxyphenyl)-*N*-methylethylamine (I). On oxidation with potassium ferricyanide 5-hydroxy-1-methylindole (III) was obtained. The mechanism of this reaction must differ from that of the conversion of the unmethylated amine into 5-hydroxyindole (Cromartie and Harley-Mason, *J.*, 1952, 2525), and it is suggested that the intermediates involved are as shown in the scheme.

* Part I, *J.*, 1954, 1165.

Synthesis of the diamine (VI; R = H, R′ = Me) was next undertaken. 2 : 5-Dimethoxyacetophenone was condensed with ethyl cyanoacetate, by the procedure devised by Cope, Hofman, Wyckoff, and Hardenburgh (*J. Amer. Chem. Soc.*, 1941, **63**, 5452), to



give ethyl 1-cyano-2-(2 : 5-dimethoxyphenyl)crotonate (IV), converted by treatment with potassium cyanide into α-(2 : 5-dimethoxyphenyl)-α-methylsuccinonitrile (V). On hydrogenation of (V) over platinum oxide in the presence of hydrochloric acid 2-(2 : 5-dimethoxyphenyl)-2-methylbutane-1 : 4-diamine (VI; R = Me, R′ = H) was obtained, and



Ultra-violet absorption spectra in buffer, pH 6·8.

I. *Eseroline.* II. *Eserethole.*

(*The* $10^{-3}\varepsilon$ *values in* II *have been increased by 2 units.*)

this with 2 mol. of benzaldehyde gave a dibenzylidene derivative which when heated with methyl iodide in a sealed tube gave the *NN′*-dimethyl derivative (VI; R = R′ = Me). This was de-*O*-methylated by boiling hydrobromic acid. Excellent yields were obtained in all the above stages. On treatment with potassium ferricyanide the dihydroxy-amine (VI; R = H, R′ = Me) gave in 30% yield a product whose properties were identical with those of (±)-eseroline (VII; R = H) (Kobayashi, *Annalen*, 1938, **536**, 143; Julian and Pikl, *J. Amer. Chem. Soc.*, 1935, **57**, 563). Identity was rigorously confirmed by ethylation with ethyl toluene-*p*-sulphonate to give (±)-eserethole (VII; R = Et), characterised as the known picrate and methopicrate. Furthermore, the ultra-violet and infra-red absorption spectra (in solution) of our product were identical with those of (−)-eseroline, prepared from the natural alkaloid. Since (±)-eserethole has earlier been resolved and converted into (−)-physostigmine (Kobayashi, *loc. cit.*), our process constitutes a conveniently brief formal synthesis of the natural product. The mechanism of the double ring-closure involved is of some interest; presumably an indolenine intermediate of the type (II) is formed, and the second nitrogen atom then adds on to the highly reactive double bond.

Experimental

2-(2 : 5-*Dimethoxyphenyl*)-N-*methylethylamine.* — 2-(2 : 5-Dimethoxyphenyl)ethylamine (Cromartie and Harley-Mason, *loc. cit.*) (6·7 g.) in benzene (25 c.c.) was treated with freshly distilled benzaldehyde (3·7 g.) in benzene (15 c.c.); heat was evolved and water separated. The benzene and water were removed under vacuum on the water-bath, the crude benzylidene

derivative was treated with methyl iodide (5·3 g.), and the mixture heated at 100° in a sealed tube for 2 hr. The solid product was extracted with 90% ethanol (50 c.c.), the solvent removed, and the residue taken up in warm dilute hydrochloric acid (25 c.c.). Benzaldehyde was removed by repeated ether extraction, and the aqueous layer was then basified and the amine extracted with ether. Solvent was removed from the dried (K_2CO_3) extracts and the residual 2-(2 : 5-dimethoxyphenyl)-*N*-methylethylamine distilled at 0·2 mm. (bath temp. 140°). The *hydrochloride* formed prisms, m. p. 96—97°, from ethanol–ether (Found: C, 56·7; H, 7·9; N, 6·2. $C_{11}H_{17}O_2N$,HCl requires C, 57·0; H, 7·8; N, 6·1%).

5-Hydroxy-1-methylindole.—The foregoing amine (2·5 g.) was refluxed with redistilled hydrobromic acid (15 c.c.; *d* 1·49) for 45 min. Evaporation of the resulting solution under reduced pressure of hydrogen gave the dihydroxy-amine hydrobromide as a brown glass.

A solution of the hydrobromide (0·77 g.) in water (50 c.c.) was stirred vigorously with ethyl acetate (100 c.c.) during the slow addition (45 min.) of potassium ferricyanide (2·05 g.) and sodium hydrogen carbonate (0·8 g.) in water (50 c.c.). The colour of the solution changed to deep brown and some dark flocculent precipitate separated, causing the mixture to form an emulsion. A little sodium dithionite was added and, after filtration through "Hyflo," the layers were separated and the aqueous layer again extracted with ethyl acetate. The combined ethyl acetate extracts were dried ($MgSO_4$) and the solvent removed under hydrogen leaving a brown gum. Sublimation at 115°/10^{-4} mm. followed by recrystallisation from light petroleum (b. p. 80—100°) gave *5-hydroxy-1-methylindole* as needles, m. p. 131—132° (Found: C, 71·8, 73·5; H, 6·1, 6·7; N, 9·7. C_9H_9ON requires C, 73·4; H, 6·1; N, 9·5%). Better figures for carbon and hydrogen could not be obtained; the ultra-violet absorption spectrum, measured in 95% ethanol ($\lambda_{max.}$ 3040, 2760 Å; $\varepsilon_{max.}$ 4000, 6680: $\lambda_{min.}$ 2920, 2480 Å; $\varepsilon_{min.}$ 3540, 2270) was very similar to that of 5-hydroxyindole ($\lambda_{max.}$ 2970, 2700 Å; $\varepsilon_{max.}$ 3100, 5700: $\lambda_{min.}$ 2920, 2450; $\varepsilon_{min.}$ 2920, 1550).

α-(2 : 5-Dimethoxyphenyl)-α-methylsuccinonitrile (V).—2 : 5-Dimethoxyacetophenone (18 g.), ethyl cyanoacetate (11·3 g.), ammonium acetate (1·5 g.), and acetic acid (4·8 g.) in benzene (50 c.c.) were refluxed for 5 hr. in a flask attached to a Dean and Stark separator (cf. Cope *et al.*, *loc. cit.*). The cooled mixture was washed with water (2 × 50 c.c.), and the benzene removed. The residual *ethyl 1-cyano-2-(2 : 5-dimethoxyphenyl)crotonate* (IV) (22 g., 80%) distilled at 160—165°/0·3 mm. as a very viscous yellow oil (Found: C, 65·3; H, 6·1. $C_{15}H_{17}O_4N$ requires C, 65·5; H, 6·2%).

The foregoing ester (10 g.) and "AnalaR" potassium cyanide (4·3 g.) in 90% ethanol (120 c.c.) were refluxed for 2 hr. The resulting orange solution was cooled, the separated potassium carbonate filtered off, and the filtrate evaporated to dryness under vacuum. The oily residue crystallised slowly and was recrystallised from aqueous ethanol (charcoal), giving *α-(2 : 5-dimethoxyphenyl)-α-methylsuccinonitrile* (6·6 g., 80%) as prisms, m. p. 70° (Found: C, 68·3; H, 5·7; N, 12·2. $C_{13}H_{14}O_2N_2$ requires C, 67·7; H, 6·1; N, 12·2%). The nitrile was characterised by boiling a small amount with concentrated hydrochloric acid for 15 hr.; *α-(2 : 5-dimethoxyphenyl)-α-methylsuccinic acid* formed prisms, m. p. 163—164°, from aqueous ethanol (Found: C, 58·3; H, 5·9. $C_{13}H_{16}O_6$ requires C, 58·2; H, 6·0%).

2-(2 : 5-Dimethoxyphenyl)-2-methylbutane-1 : 4-diamine (VI; R = Me, R′ = H).—The succinonitrile (5·0 g.), dissolved in ethanol (190 c.c.) and concentrated hydrochloric acid (10 c.c.), was hydrogenated at 4—5 atm. over Adams's platinum oxide (0·5 g.). Hydrogen uptake (4 mol.) was complete in 10—15 hr., and, after filtration from the catalyst, the solution was evaporated to dryness under vacuum. The viscous residue was triturated with a little propanol and ether, and slowly crystallised at 0°. Recrystallised from propanol–ether, *2-(2 : 5-dimethoxyphenyl)-2-methylbutane-1 : 4-diamine dihydrochloride* (6 g., 90%) formed prisms, m. p. 173—174° (Found: N, 9·2. $C_{13}H_{22}O_2N_2$,2HCl requires N, 9·0%). The *dipicrate* formed yellow needles, m. p. 201—202°, from aqueous ethanol (Found: C, 42·9; H, 4·3; N, 15·9. $C_{13}H_{22}O_2N_2$,$2C_6H_3O_7N_3$ requires C, 43·1; H, 4·0; N, 16·1%).

2-(2 : 5-Dihydroxyphenyl)-2 : N : N′-trimethylbutane-1 : 4-diamine (VI; R = H, R′ = Me).—A solution of the above dihydrochloride (7 g.) in water (20 c.c.) was basified, saturated with potassium carbonate, and extracted with ether. The extract was dried (K_2CO_3), the ether removed, and the residual diamine (4·7 g.) dissolved in benzene (25 c.c.). A solution of freshly distilled benzaldehyde (4·2 g.) in benzene (25 c.c.) was then added. The benzene and water were removed under vaccum, and the residual viscous brown oil slowly solidified. A small portion was recrystallised by allowing a solution in ether–light petroleum to evaporate slowly, giving the *dibenzylidene* derivative as stout needles, m. p. 69° (Found: C, 77·7; H, 6·8; N, 6·6. $C_{27}H_{30}O_2N_2$ requires C, 78·2; H, 7·3; N, 6·7%).

The major portion was treated with methyl iodide (5·6 g.) at 100° for 2 hr. in a sealed tube. The solid product was extracted with 90% ethanol (50 c.c.), the solvent removed on the water-bath, and the residue taken up in dilute hydrochloric acid (30 c.c.). Benzaldehyde was removed by repeated ether extraction, and the aqueous layer then basified, saturated with potassium carbonate, and extracted with ether (3 × 50 c.c.). The extract was dried (K_2CO_3), the solvent removed, and the residual diamine (4·1 g., 70%) distilled at 155—160°/2 mm. The *dipicrate* formed yellow platelets, m. p. 105—106°, from aqueous ethanol (Found: C, 43·8; H, 4·3; N, 15·2. $C_{15}H_{26}O_2N_2,2C_6H_3O_7N_3,H_2O$ requires C, 43·6; H, 4·6; N, 15·1%).

The foregoing diamine (4 g.) and redistilled hydrobromic acid (25 c.c.; *d* 1·49) were refluxed for 45 min., and the solution was diluted with water, boiled with charcoal, and evaporated to dryness under reduced pressure of hydrogen. The solid residue was triturated with a little propanol and ether, giving the *dihydrobromide* (5·4 g., 90%) as small prisms; it had m. p. 235—237° (from propanol–ether) (Found: C, 38·8; H, 5·6; N, 7·1. $C_{13}H_{22}O_2N_2,2HBr$ requires C, 39·0; H, 6·0; N, 7·0%).

(±)-*Eseroline* (VII; R = H).—The dihydrobromide (1·2 g.) in water (75 c.c.) was stirred under nitrogen during the slow addition (30 min.) of a solution of potassium ferricyanide (1·95 g.) and sodium hydrogen carbonate (1·02 g.) in water (75 c.c.). The deep reddish-violet solution thus obtained was immediately transferred to a continuous extractor and extracted with peroxide-free ether under nitrogen for 30 hr., during which time the colour slowly faded. The ethereal extract was evaporated to dryness, leaving crude (±)-eseroline (0·49 g.; 75%) as a brown gum, which was dissolved in benzene; addition of light petroleum precipitated some dark brown amorphous impurities. The filtrate was evaporated to dryness, and the residue sublimed at 120°/10^{-4} mm., giving (±)-eseroline (0·2 g.) as prisms, m. p. 136—137° (Found: C, 71·7; H, 8·1; N, 13·2. Calc. for $C_{13}H_{18}ON_2$: C, 71·5; H, 8·3; N, 12·8%). Julian and Pikl (*loc. cit.*) give m. p. 138°; Kobayashi (*loc. cit.*) gives m. p. 137—138°. The ultra-violet absorption spectrum (see Figure) in aqueous buffer at pH 6·8 was identical with that of (−)-eseroline, prepared according to Ellis and Jones (*J. Pharm. Exp. Therap.*, **1943**, **79**, 364). The infra-red absorption spectra of the natural and synthetic products in carbon tetrachloride and carbon disulphide solution were also identical.

(±)-*Eserethole*.—Crude (±)-eseroline (0·48 g.) in absolute ethanol (40 c.c.) and a solution of sodium ethoxide [from sodium (0·1 g.) in ethanol (10 c.c.)] were refluxed under nitrogen with ethyl toluene-*p*-sulphonate (0·47 g.) for 4 hr. The ethanol was removed and the residue treated with dilute sodium hydroxide solution (25 c.c.), saturated with potassium carbonate, and extracted with ether (3 × 50 c.c.). The dried (K_2CO_3) extracts were evaporated and the brown residue distilled at 1 mm. (bath temp. 120°) giving (±)-eserethole as a pale yellow oil. The ultra-violet absorption spectrum was identical with that of (−)-eserethole (see Figure). The picrate formed orange needles, m. p. 154° (Found: C, 52·8; H, 5·3; N, 15·1. Calc. for $C_{15}H_{22}ON_2,C_6H_3O_7N_3$: C, 53·0; H, 5·3; N, 14·7%). Julian and Pikl (*loc. cit.*) give m. p. 155°. The methopicrate was prepared following the latter authors and formed red prisms, m. p. 190—191° (decomp.) (Found: C, 53·6; H, 5·3; N, 14·6. Calc. for $C_{16}H_{24}ON_2,C_6H_3O_7N_3$: C, 53·3; H, 5·6; N, 14·3%). Hoshino, Kobayashi, and Kotake (*Annalen*, 1935, **516**, 81) give m. p. 191—192°, Julian and Pikl (*loc. cit.*) give m. p. 194°.

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Synthesis of 2 : 2″-Dimethoxy-o-terphenyl and Some Related Substances.

By R. L. Huang.

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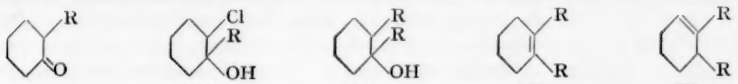
2 : 2″-Dimethoxy-*o*-terphenyl has been prepared. If restricted rotation were operative, this should exist in two forms, but only one was obtained.

Since the benzene rings in *o*-terphenyl are non-planar (Pickett, Walter, and France, *J. Amer. Chem. Soc.*, **1936**, **58**, 2296; Merkel and Wiegand, *Z. Naturforsch.*, **1948**, **3**b, 93), a derivative of it containing an *ortho*- or a *meta*-substituent in each of the peripheral rings might, by restricted rotation, exist in two geometrical isomers in which the substituents are "*cis*" or "*trans*" to each other with respect to the central ring. We have synthesised such a compound, in which the two substituents are *o*-methoxy : although Fisher–Taylor–Hirschfelder models indicate that rotation is restricted, only one form has been isolated.

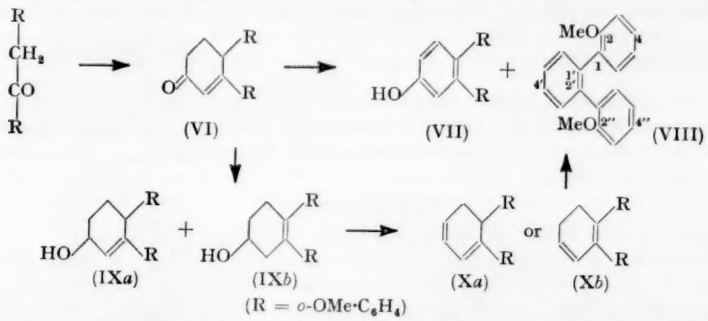
Reaction of 2-chloro*cyclo*hexanone with *p*-methoxyphenylmagnesium bromide gave a fair yield of the ketone (I; R = *p*-MeO·C_6H_4) (Bachmann, Fujimoto, and Wick, *J. Amer. Chem. Soc.*, **1950**, **72**, 1995), but use of *o*-methoxyphenylmagnesium bromide furnished only the chlorohydrin (II) and traces of the alcohol (III) (Huang, *J. Org. Chem.*, 1954, **19**, 1363). Prolonged heating, in *p*-xylene, of the magnesium complex formed from the Grignard reagent and the chloro-ketone gave a modest yield of a mixture of the diaryl-*cyclo*hexenes (IV and V) (cf. Mueller and Pickens, *J. Amer. Chem. Soc.*, 1950, **72**, 3626), but this mixture could not be dehydrogenated by sulphur or palladium–charcoal. Heating the alcohol (III) with palladised charcoal caused only dehydration.



(I) (II) (III) (IV) (V)

(R = *o*-OMe·C_6H_4 unless otherwise specified)

2 : 2′-Dimethoxydeoxybenzoin, prepared in three steps from salicylaldehyde, condensed with 4-diethylaminobutan-2-one in presence of sodium ethoxide (cf. Dodds, Huang, Lawson, and Robinson, *Proc. Roy. Soc.*, 1953, *B*, **140**, 470) to give the diaryl*cyclo*hexenone (VI) in 52—56% yield. On dehydrogenation at 180—300° this gave approximately 4 parts of the phenol (VII) and 1 part of 2 : 2″-dimethoxy-*o*-terphenyl (VIII), the latter being always a



(VI) (VII) (VIII)

(IX*a*) (IX*b*) (X*a*) (X*b*)

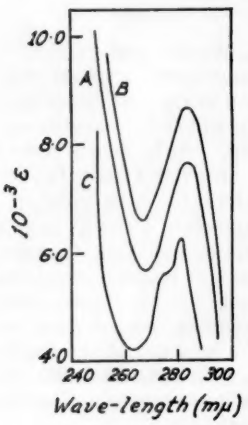
(R = *o*-OMe·C_6H_4)

homogeneous single compound. Since the postulated isomers would differ in thermal stability, milder methods for this transformation were tried, including catalytic dehydrogenation in lower-boiling solvents, *e.g.*, *p*-xylene and cumene, but these proved ineffective.

Lithium aluminium hydride reduced the *cyclo*hexenone (VI) at 28° (reaction was incomplete at 0°) to a mixture containing small amounts of diaryl*cyclo*hexenol and the diaryl*cyclo*hexene (IV). The former product was a mixture, perhaps of structural isomers (IX*a* and *b*) as well as of stereoisomers, and no homogeneous individual was isolated.

Reduction by aluminium *iso*propoxide in *iso*propyl alcohol gave a much better yield (58%) of a similar inseparable mixture of diaryl*cyclo*hexenols; prolonged heating of the reaction mixture did not cause double-bond migration leading to a single product (cf. Heilbron, Kennedy, Spring, and Swain, *J.*, 1938, 869).

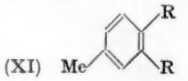
When the mixture of *cyclo*hexenols was dehydrated by potassium hydrogen sulphate in boiling *p*-xylene and the crude product dehydrogenated with palladised charcoal in the same solvent, there were obtained, after chromatography and crystallisation, only the same terphenyl as previously and a small amount of the *cyclo*hexadiene (X*a* or *b*). When the temperature of dehydrogenation was reduced, by use of benzene instead of xylene, approximately equal quantities of the same two substances were isolated. The diene was converted into the same terphenyl by further dehydrogenation: the relatively small tendency to aromatisation is probably due to the lack of coplanarity, and so of resonance, of the benzene rings of the terphenyl.

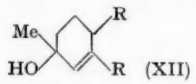


A, 2 : 2''-*Dimethoxy*-o-*ter*-*phenyl*. *B*, 2 : 2''-*Di*-*methoxy*-4'-*methyl*-o-*ter*-*phenyl*. *C*, 1 : 2-*Di*-o-*methoxyphenyl*cyclo*hexa*-*diene*.

The postulated isomerism might be shown, not merely by the terphenyl (VIII), but also by the phenol (VII) and by the methyl derivative (XI). The phenol (VII), derived from the *cyclo*hexenone (VI) by dehydrogenation (see above), was obtained in only one form. Attempts were therefore made to secure the postulated isomer by varying the conditions of the aromatisation of (VI), the phenyl homologue (VI, R = Ph) being also prepared (Dodds *et al.*, *loc. cit.*) for use as a model. However, bromination of these *cyclo*hexenones with bromine in acetic acid or with *N*-bromosuccinimide, followed by dehydrobromination with pyridine, led to intractable oils.

In the synthesis of the methyl derivative (XI), the *cyclo*hexenone (VI) reacted stereospecifically with methylmagnesium iodide to give only one form of the alcohol (XII) which was readily dehydrated but could be obtained pure by using a slight excess of magnesium and excluding acidic or other dehydrating agents during its isolation. Conversion of this alcohol into the terphenyl (XI) by dehydration and dehydrogenation was effected in one operation, by heating it with palladised charcoal at 275°, in boiling *p*-xylene, or in boiling *p*-cymene. Again only one form of the terphenyl was obtained.





(R = *o*-OMe·C_6H_4)

Very similar absorption spectra were observed for 2 : 2''-dimethoxy-*o*-terphenyl (VIII) ($\lambda_{max.}$ 283 mμ; ε 7680) and 2 : 2''-dimethoxy-4'-methyl-*o*-terphenyl (XI) ($\lambda_{max.}$ 283; ε 8700), but that of 1 : 2-di-*o*-methoxyphenyl*cyclo*hexadiene (X*a* or *b*) ($\lambda_{max.}$ 281; ε 6240) was different in type (see Figure).

Experimental

Some of the analyses are by Dr. W. Zimmermann, University of Melbourne.

1 : 2-*Di*-o-*methoxyphenyl*cyclo*hexene*.—2-Chloro*cyclo*hexanone (21 g.) in ether (50 c.c.) was added during 20 min. to a stirred solution of *o*-methoxyphenylmagnesium bromide, prepared from *o*-bromoanisole (34 g.) and magnesium (4·4 g.) in ether (100 c.c.). Heat was evolved causing gentle reflux during the addition. Xylene (100 c.c.) was then introduced, the ether removed, and the resulting mixture heated under reflux and with stirring for 20 hr. It was then poured into a saturated solution of ammonium chloride and the organic matter isolated by extraction with ether, washed with ammonium chloride solution and water, dried, and concentrated. Fractionation of the product gave the diaryl*cyclo*hexene (probably a mixture of isomers) as a pale yellow viscous oil, b. p. 168—180°/1 mm. (6 g.), n_D^{29} 1·5801 [Found: C, 81·5; H, 7·4; *M* (cryoscopic), 261. Calc. for $C_{20}H_{22}O_2$: C, 81·6; H, 7·5; *M*, 294], soluble in light petroleum and ethanol.

Attempted dehydrogenation. The above *cyclo*hexene (1·3 g.; freshly redistilled) and 5% palladised charcoal (0·4 g.) were heated in nitrogen to 280° for 40 min. and finally to 300° for 20 min. The product was adsorbed on a column of alumina and eluted with light petroleum–benzene and finally with benzene, giving twenty fractions, none of them crystalline. Dehydrogenation with sulphur at 230° for 30 min. was also unsuccessful.

Dehydrogenation of 1 : 2-*Di*-o-*methoxyphenyl*cyclo*hexanol.*—The *cyclo*hexanol (0·3 g.) (Huang, *loc. cit.*) was heated with palladised charcoal at 300—320° for 30 min. in carbon dioxide. The product gave a yellow oil, b. p. 145° (bath)/0·2 mm. (Found: C, 80·9; H, 7·4%), which was apparently a mixture of the *cyclo*hexenes.

2 : 2′-*Dimethoxydeoxybenzoin.*—2 : 2′-Dimethoxybenzoin was reduced with a tin–copper couple (Allen and Buck, *J. Amer. Chem. Soc.*, 1930, **52**, 312). The product was best isolated by extraction with benzene, and crystallised from light petroleum (b. p. 60—80°) (yield, 50%).

3 : 4-*Di*-o-*methoxyphenyl*cyclo*hex*-2-*en*-1-*one.*—2 : 2′-Dimethoxydeoxybenzoin (36 g.), dissolved in a mixture of dry benzene (125 c.c.) and absolute ethanol (25 c.c.), was added to the methiodide prepared from methyl iodide (21 g.) and 4-diethylaminobutan-2-one (21 g.) (Wilds and Shunk, *ibid.*, 1943, **65**, 469) cooled in ice and under an atmosphere of nitrogen. A solution from sodium (6·8 g.) in ethanol (150 c.c.) was added during 1 hr. with ice-cooling, the mixture being then kept at *ca.* 10° for one more hour during which the methiodide gradually disappeared. The mixture was then warmed to the b. p. (*ca.* ½ hr.) and allowed to boil gently for 15 min., after which it was poured on cracked ice containing a slight excess of sulphuric acid. The organic matter was taken up in ether, washed with water, dried, and concentrated. The product passed in benzene through alumina, giving the required cyclo*hexenone* as pale yellow prisms, m. p. 111—115° (24 g.) raised to 115—117° by recrystallisation from benzene–*cyclo*hexane (Found: C, 78·1; H, 6·7. $C_{29}H_{20}O_3$ requires C, 77·9; H, 6·5%). It was very soluble in benzene and ethanol, but only slightly so in *cyclo*hexane. The 2 : 4-*dinitrophenylhydrazone*, formed readily with Brady's reagent, crystallised from glacial acetic acid in deep red leaflets, m. p. 211—213° (Found: C, 63·7; H, 4·75. $C_{26}H_{24}O_6N_4$ requires C, 63·9; H, 4·95%).

Dehydrogenation experiments. The above *cyclo*hexenone was treated with Raney nickel in boiling ethanol before the following dehydrogenation experiments.

(i) Refluxing with 5% palladised charcoal in ethylbenzene for 36 hr. or with Adams catalyst in *p*-xylene for 72 hr. gave no phenol. Refluxing with palladised charcoal in cumene for 60 hr. gave a small quantity of phenol. In each case most of the starting material was recovered.

(ii) The *cyclo*hexenone was heated with palladised charcoal under carbon dioxide at (*a*) 210—240°, (*b*) 270—280°, and (*c*) 290—300° for 1—1½ hr. For (*b*), a typical experiment, the *cyclo*hexenone (1·0 g.) gave a solid, m. p. *ca.* 138—142° (0·78 g.), which did not react with 2 : 4-dinitrophenylhydrazine and yielded after repeated crystallisations from benzene 2 : 2″-*dimethoxy*-4′-*hydroxy*-o-*terphenyl* as prisms, m. p. 169—170° (*ca.* 0·3 g.) (Found: C, 78·6; H, 6·15. $C_{20}H_{18}O_3$ requires C, 78·4; H, 5·9%). This was very soluble in ethanol, but much less so in benzene or *cyclo*hexane, and did not dissolve in aqueous potassium hydroxide even on heating. Crops obtained from the mother-liquors were repeatedly crystallised from ethanol, giving 2 : 2″-*dimethoxy*-o-*terphenyl* in rhombic plates, m. p. 109—110·5° (*ca.* 80 mg.) (Found: C, 82·3; H, 6·4. $C_{20}H_{18}O_2$ requires C, 82·7; H, 6·3%), very soluble in benzene, but much less so in ethanol and decolorising bromine readily in chloroform.

Reduction with Lithium Aluminium Hydride.—(*a*) Reduction at 0° for 0·5 hr. leaves most of the preceding *cyclo*hexenone unchanged (2 : 4-dinitrophenylhydrazone). (*b*) Lithium aluminium hydride (2 g.) was added to the *cyclo*hexenone (5·0 g.) in ether (150 c.c.) at 15°, and the mixture stirred for 2 hr. at room temperature (28°). Moist ether was then added, followed by water and dilute sulphuric acid. The product was taken up in ether, washed with water, and dried, and the ether removed, giving an oil which was very soluble in benzene and ethanol but sparingly so in *cyclo*hexane and petroleum; on slow fractional crystallisation from benzene–*cyclo*hexane this yielded 3 : 4-di-*o*-methoxyphenyl*cyclo*hex-2-en-1-ol (probably with other isomers), m. p. 87—89°, with preliminary softening. Repeated crystallisations from the same solvents gave solids of varying m. p.s (87—92°) which depended on the rate of heating (Found: C, 76·9; H, 6·9. Calc. for $C_{20}H_{22}O_3$: C, 77·4; H, 7·1%). The mother-liquors deposited another solid, probably 1 : 2-*di*-o-*methoxyphenyl*cyclo*hexene*, m. p. 173—177° (0·3 g.) raised to 184—185° after further recrystallisation from benzene–ethanol from which it separated in prisms (Found: C, 81·9; H, 7·4. $C_{20}H_{22}O_2$ requires C, 81·6; H, 7·5%).

Meerwein–Pondorff Reduction.—The *cyclo*hexenone (3·8 g.) was heated with aluminium *iso*propoxide (12 g.) and dry *iso*propyl alcohol (60 c.c.) for 24 hr. under a fractionating column at such a rate that the acetone produced was slowly removed. The mixture was poured into

ice and dilute hydrochloric acid, and the organic material extracted into benzene, washed with dilute hydrochloric acid, water, and aqueous sodium carbonate, and dried. Evaporation of most of the benzene gave an oil which did not react with 2 : 4-dinitrophenylhydrazine and, on addition of *cyclo*hexane, gradually deposited the *cyclo*hexenol as a colourless solid, m. p. 85—88° (2·2 g.). A recrystallised sample (m. p. 87—89°) did not depress the m. p. of the product from the previous reduction (Found : C, 77·6; H, 7·2%).

Dehydration of the Isomeric cyclo*Hexenols.*—(*a*) On addition of phosphoric anhydride (3 g.) to a solution of the *cyclo*hexenols (1·4 g.) in hot benzene (25 c.c.) a green colour developed which soon darkened. The solution was heated under reflux for 6 hr. Chromatography (twelve fractions) gave small quantities of yellow amorphous substances of indefinite m. p.s.

(*b*) The mixture of *cyclo*hexenols (1·5 g.) was heated under reflux with freshly fused potassium hydrogen sulphate (1·5 g.) in benzene (10 c.c.) for 24 hr., more sulphate (1 g.) being added after the first 10 hr. Water was then introduced and the benzene layer separated. The aqueous layer was extracted with fresh benzene, and the combined organic fractions were washed with a solution of sodium hydrogen carbonate and with water, dried, and concentrated to about 15 c.c. After addition of 5%-palladised charcoal (*ca.* 0·5 g.) the mixture was refluxed for another 24 hr. during which time a second lot of the catalyst (*ca.* 0·5 g.) was added. The product was adsorbed on alumina, and eluted with light petroleum (b. p. 60—80°)–benzene (1 : 1). Fractions 1—4 (15 c.c. each) on evaporation yielded crystalline solids which were separately recrystallised from ethanol, giving two substances A and B. Very small quantities of amorphous substances of indefinite m. p. were found in some of the later fractions (4—15), which were not investigated.

Substance A (0·38 g.) was the less soluble in ethanol and was found to be identical with the 2 : 2''-dimethoxy-*o*-terphenyl obtained previously (m. p. and mixed m. p. 109—110°) (Found : C, 83·0; H, 6·3%). It was unaffected by irradiation with ultra-violet light in benzene solution for 7 hr. Demethylation by refluxing hydriodic acid (*d* 1·7)–acetic acid (1 : 2) for 4 hr. gave 2 : 2''-*dihydroxy*-o-*terphenyl*, soluble in cold aqueous potassium hydroxide and crystallising from benzene in needles, m. p. 148—150° (Found : C, 82·6; H, 5·3. $C_{18}H_{14}O_2$ requires C, 82·4; H, 5·4%).

Substance B which was present in comparatively larger quantities in the first two fractions, was obtained from the mother-liquors of the ethanol recrystallisations. It had m. p. 84—87° (0·34 g.), raised to 85·5—87° after four recrystallisations from ethanol, and was found to be 1 : 2-*di*-o-*methoxyphenyl*cyclo*hexa*-1 : 3-*diene*, or an isomer thereof (Found : C, 82·3, 81·8; H, 6·9, 7·1; O, 10·4. $C_{20}H_{20}O_2$ requires C, 82·15; H, 6·9; O, 10·95%). It was very soluble in benzene and *cyclo*hexane, and decolorised bromine instantaneously. With palladised charcoal in boiling *p*-xylene (bath 160°) (14 hr.) it was converted quantitatively into substance A (m. p. and mixed m. p.).

3 : 4-*Di*-o-*methoxyphenyl*-1-*methyl*cyclo*hex*-2-*en*-1-*ol*.—3 : 4-Di-*o*-methoxyphenyl*cyclo*hex-2-en-1-one (3·0 g.) in ether (120 c.c.) was added to the Grignard reagent prepared from methyl iodide (14 g.) and magnesium (2·7 g.) in ether (75 c.c.) during ½ hr., and the mixture was stirred under gentle reflux for a further 2 hr. Next day it was poured into ice and water containing a trace of sodium hydrogen sulphite, and further treated with a saturated solution of ammonium chloride. The organic matter was extracted in ether in the usual manner, giving an oil which in contact with light petroleum deposited the cyclo*hexenol*, m. p. *ca.* 110—112° (1·9 g.), raised to 122—124° after four recrystallisations (leaflets) from *cyclo*hexane (Found : C, 77·5; H, 7·5. $C_{21}H_{24}O_3$ requires C, 77·75; H, 7·5%).

Dehydration and dehydrogenation. The *cyclo*hexenol was heated with 5% palladised charcoal (*a*) at 275° for 45 min., without a solvent, (*b*) in refluxing *p*-cymene for 7 hr., under nitrogen, and (*c*) in *p*-xylene for 44 hr. In each case *ca.* 60% of 2 : 2''-*dimethoxy*-4'-*methyl*-o-*terphenyl* was obtained, which crystallised from ethanol in prisms, m. p. 85—86°, and reacted with bromine rapidly (Found : C, 82·85, 82·7; H, 6·6, 6·7. $C_{21}H_{20}O_2$ requires C, 82·9; H, 6·6%). In (*a*) it was necessary to chromatograph the product before the pure hydrocarbon could be obtained. When heated in benzene with anhydrous copper sulphate for 7 hr. and then with palladised charcoal for 24 hr., or with potassium hydrogen sulphate in *p*-xylene for 12 hr. and then with palladised charcoal for 12 hr., the *cyclo*hexenol gave no crystalline product.

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The Preparation of Polycyclic Aromatic Hydrocarbons from Arylpropiolic Acids.

By A. D. CAMPBELL.

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2 : 3-Benzoperylene (III), naphtho(2′ : 3′-1 : 2)pyrene (VI), 1 : 2-3 : 4-5 : 5*a* : 6-11 : 11*a* : 12-tetrabenzonaphthacene (X), and 1 : 2-benzopyrene (XIII) have been synthesised by decarboxylation and cyclodehydrogenation of the products of dimerisation of a series of β-arylpropiolic acids. Several fluorenones have been prepared by decarboxylation of the acids obtained by intramolecular cyclisation of the dimerisation products.

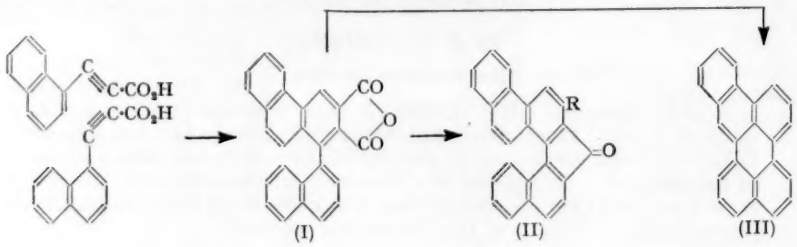
THE dimerisation of β-phenylpropiolic acid with acetic anhydride was first reported by Michael and Bucher (*Annalen*, 1895, **28**, 2511) who later (*Amer. Chem. J.*, 1898, **20**, 89) proved the product to be 1-phenylnaphthalene-2 : 3-dicarboxylic anhydride. In later papers Bucher (*J. Amer. Chem. Soc.*, 1908, **30**, 1244; 1910, **32**, 212), Haworth and Sheldrick (*J.*, 1935, 636), Haworth and Kelly (*J.*, 1936, 745), and Baddar and his co-workers (*J.*, 1947, 224; 1948, 1267; 1951, 1844) extended the reaction to substituted phenylpropiolic acids where the structures of many of the products have been proved by alternative syntheses and by degradation. The dimerisation of β-1-naphthylpropiolic acid to give 1-1′-naphthylphenanthrene-2 : 3-dicarboxylic anhydride (I), reported by West (*J. Amer. Chem. Soc.*, 1920, **42**, 1656) and Wojack, Glupe, and Jatzkewitz (*Ber.*, 1938, **71**, 1372), is the only example of this reaction with a polycyclic β-arylpropiolic acid.

In the present work β-arylpropiolic acids (aryl = Ph, 1- and 2-naphthyl, and 9-phenanthryl) were prepared by bromination, followed by dehydrobromination, of the corresponding acrylic acids (Willstaedt and Scheiber, *Ber.*, 1934, **67**, 466; Wojack *et al.*, *loc. cit.*; Reimer, *J. Amer. Chem. Soc.*, 1942, **64**, 2510). Bromination of β-(5 : 6 : 7 : 8-tetrahydro-2-naphthyl)acrylic acid with bromine in carbon tetrachloride or with pyridine hydrobromide perbromide (Rosemund and Kuhnhenn, *Ber.*, 1923, **56**, 1262) took place with the evolution of hydrogen bromide to give, in the latter case, a crystalline dibromo-acid where replacement of hydrogen had taken place. The required tetrahydronaphthylpropiolic acid was synthesised by carboxylation of the Grignard derivative of 6-ethynyl-1 : 2 : 3 : 4-tetrahydronaphthalene which was prepared from 6-acetyl-1 : 2 : 3 : 4-tetrahydronaphthalene by treatment with phosphorus pentachloride followed by dehydrohalogenation.

Refluxing β-1-naphthylpropiolic acid with acetic anhydride gave the dimer, 1-1′-naphthylphenanthrene-2 : 3-dicarboxylic anhydride (I), m. p. 232°, which is much higher than that previously reported by West (*loc. cit.*; m. p. 207—209°) and Wojack *et al.* (*loc. cit.*; m. p. 206°). The insoluble potassium salt derived therefrom was decarboxylated when heated with soda-lime and copper powder under reduced pressure, to give a mixture of 2 : 3-benzoperylene (III), formed by simultaneous dehydrogenation, and 1-1′-naphthylphenanthrene. These products were not readily separated by chromatography, but were separated by means of their 1 : 3 : 5-trinitrobenzene complexes. The two hydrocarbons were also obtained, but in lower yield, by direct distillation of the dry sodium salt formed from the anhydride. Bachmann and Deno (*J. Amer. Chem. Soc.*, 1949, **71**, 3062) prepared 1-1′-naphthylphenanthrene by the dimerisation of 1-vinylnaphthalene to 1 : 2 : 3 : 4-tetrahydro-1-naphthylphenanthrene, followed by dehydrogenation. The absorption spectrum of 2 : 3-benzoperylene (Fig. 1*C*) shows similarities to those of perylene (Clar, *Spectrochim. Acta*, 1950, **4**, 119) and 2 : 3-8 : 9-dibenzoperylene (Clar, *Ber.*, 1932, **65**, 848).

No cyclisation took place on treatment of 1-1′-naphthylphenanthrene-2 : 3-dicarboxylic anhydride (I) with anhydrous hydrogen fluoride although the isomeric 4-2′-naphthylphenanthrene-2 : 3-dicarboxylic anhydride (IV) gave a fluorenone under similar conditions (see below). Cyclisation of the anhydride (I) with aluminium chloride in nitrobenzene gave a good yield of the very sparingly soluble 9-oxo-5 : 6-benzonaphtho(1′ : 2′-3 : 4)-fluorene-1-carboxylic acid (II; R = CO_2H) which was readily decarboxylated to the brick-

red 5 : 6-benzonaphtho(1′ : 2′-3 : 4)fluorenone (II; R = H). The carbonyl ring of the latter compound was opened by fusion with potassium hydroxide to give a carboxylic acid which was decarboxylated to 1-1′-naphthylphenanthrene.



Dimerisation of β-2-naphthylpropiolic acid with acetic anhydride gave excellent yields of 4-2′-naphthylphenanthrene-2 : 3-dicarboxylic anhydride (IV). Chromatographic separation of the products obtained by direct decarboxylation of this anhydride by sublim-

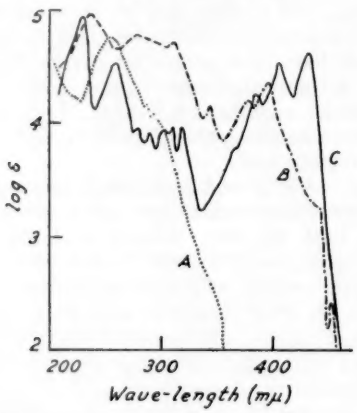


FIG. 1. *Absorption spectra of*: *A*, 1-9′-*phenanthryltriphenylene in* 95% *ethanol*; *B*, 1 : 2-3 : 4-5 : 5*a* : 6-11 : 11*a* : 12-*tetrabenzonaphthacene* (X) – – – – – *in benzene*, — · — · — *in* 95% *ethanol*; *and C*, 2 : 3-*benzoperylene* (III) *in* 95% *ethanol*.

ation from copper bronze and soda-lime under reduced pressure gave 4-2′-naphthylphenanthrene together with two isomeric ketones which are probably 7 : 8- (V; R = H) and 6 : 7-benzonaphtho(2′ : 1′-3 : 4)fluorenone (VII). Both these fluorenones gave potassium salts when fused with potassium hydroxide, and the acids obtained from them were decarboxylated to 4-2′-naphthylphenanthrene, showing that the ketones differ only in the point of attachment of the carbonyl group in the naphthalene nucleus. Further, both potassium salts were sublimed from copper bronze to give naphtho(2′ : 3′-1 : 2)pyrene (VI). Intramolecular cyclisation of 4-2′-naphthylphenanthrene-2 : 3-dicarboxylic anhydride with aluminium chloride in nitrobenzene or with anhydrous hydrogen fluoride gave the same keto-acid; on the assumption that normal cyclisation has taken place, with the new ring attached to the α- rather than to the β-position of the naphthalene nucleus, this compound has been given the structure of 9-oxo-7 : 8-benzonaphtho(2′ : 1′-3 : 4)fluorene-1-carboxylic acid (V; R = CO_2H). Decarboxylation with copper bronze in quinoline then gave the red 7 : 8-benzonaphtho(2′ : 1′-3 : 4)fluorenone (V; R = H), m. p. 239°. The two isomeric fluorenones were readily reduced by hydrazine hydrate (Cook and Preston, *J.*, 1944, 553) in good yield to 7 : 8-benzonaphtho(2′ : 1′-3 : 4)fluorene, and 6 : 7-benzonaphtho(2′ : 1′-3 : 4)fluorene, which had similar ultra-violet absorption spectra (Fig. 3*B* and *C*). Buu-Hoï and Cagniant (*Rev. sci.*, 1942, **80**, 436) claim to have prepared 7 : 8-benzonaphtho(2′ : 1′-3 : 4)fluorene by cyclisation of 1 : 2 : 3 : 4-tetrahydro-3-1′-naphthylmethylene-4-oxophenanthrene, but the m. p. (285°) of their product does not correspond with that of either of the hydrocarbons now obtained, and they gave no proof of their formula. Reduction of

7 : 8-benzonaphtho(2′ : 1′-3 : 4)fluorenone with zinc dust in acetic acid gave the corresponding fluorenol, which on distillation from zinc dust gave 7 : 8-benzonaphtho(2′ : 1′-3 : 4)-fluorene identical with that obtained by reducing the fluorenone with hydrazine hydrate. Cyclodehydrogenation of 4-2′-naphthylphenanthrene with aluminium chloride–sodium chloride at 140° gave only polymerised material, but at temperatures below 120° naphtho-(2′ : 3′-1 : 2)pyrene (VI) was obtained. The absorption spectrum of 4-2′-naphthylphen-

FIG. 2. *Absorption spectra of*: *A*, *4-2′-naphthylphenanthrene*; *B*, *1-1′-naphthylphenanthrene*; *and C*, *4-phenylphenanthrene*; *all in 95% ethanol.*

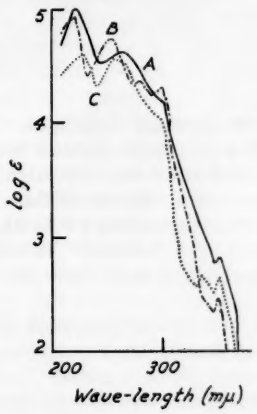
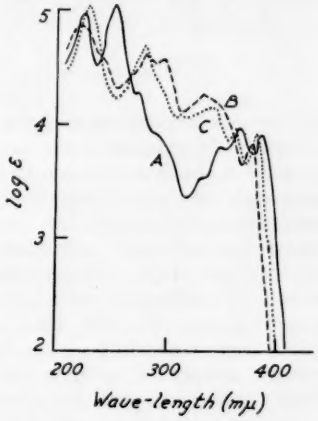
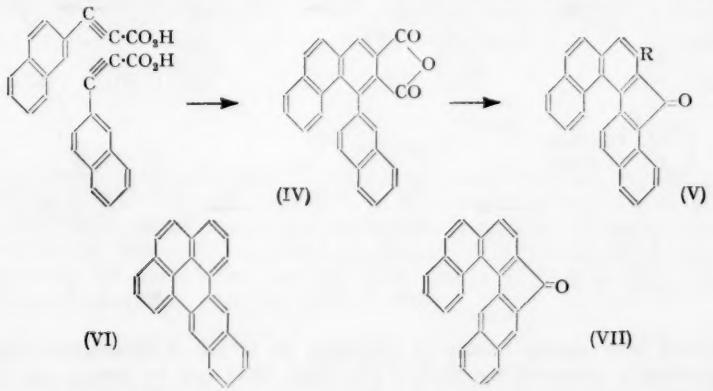


FIG. 3. *Absorption spectra of*: *A*, *1-2′-naphthylanthracene*; *B*, *7 : 8-benzonaphtho(2′ : 1′-3 : 4)fluorene*; *and C*, *6 : 7-benzonaphtho(2′ : 1′-3 : 4)fluorene*; *all in 95% ethanol.*



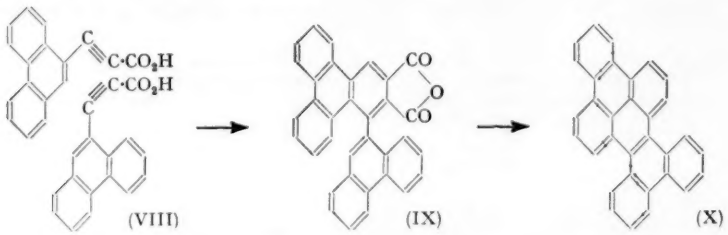
anthrene (Fig. 2*A*) resembles that of 1-1′-naphthylphenanthrene (Fig. 2*B*) (see also Bachmann and Deno, *J. Amer. Chem. Soc.*, 1949, **71**, 3062) but shows less detail.

1-9′-Phenanthryltriphenylene-2 : 3-dicarboxylic anhydride (IX), obtained by dimerising β-9-phenanthrylpropiolic acid (VIII), was decarboxylated by heating the dry sodium salt of the acid under reduced pressure with powdered soda-lime and copper powder to give a pale yellow sublimate which was chromatographed on alumina, the products being 1-9′-phenanthryltriphenylene and 1 : 2-3 : 4-5 : 5*a* : 6-11 : 11*a* : 12-tetrabenzonaphthacene



(X), the latter being formed by simultaneous decarboxylation and cyclodehydrogenation. 1-9′-Phenanthryltriphenylene, which formed a molecular complex with two molecules of 1 : 3 : 5-trinitrobenzene, gave 1 : 2-3 : 4-5 : 5*a* : 6-11 : 11*a* : 12-tetrabenzonaphthacene on

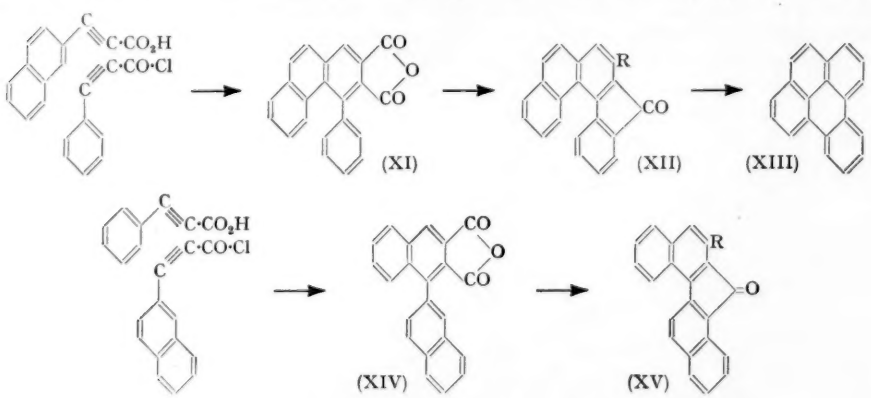
cyclodehydrogenation with palladium–charcoal. The absorption spectrum of 1-9′-phenanthryltriphenylene (Fig. 1*A*) is similar in form to the combined spectra of the two component molecules, but on cyclodehydrogenation the new hydrocarbon (X) gives a spectrum (Fig. 1*B*) showing similarity to that of 1 : 2-6 : 7-dibenzopyrene (Clar, *Ber.*, 1943, **76**, 615).



(VIII) (IX) (X)

In all the above reactions dimerisation was between identical molecules. In order to extend the scope of the reaction to the synthesis of other polycyclic systems the possibility of bringing about a reaction between two dissimilar molecules was investigated. When phenylpropiolic acid and β-2-naphthylpropiolic acid reacted a mixture of three of the four possible combinations was isolated but complete separation proved very tedious: 4-phenylphenanthrene-2 : 3-dicarboxylic anhydride (XI) formed by a " mixed " combination was isolated, together with 1-phenylnaphthalene-2 : 3-dicarboxylic anhydride and 4-2′-naphthylphenanthrene-2 : 3-dicarboxylic anhydride.

Baddar and El-Assal (*J.*, 1951, 1844) treated *o*-methoxyphenylpropiolyl chloride with phenylpropiolic acid, to obtain 1-*o*-methoxyphenyl- and 5-methoxy-1-phenyl-naphthalene-2 : 3-dicarboxylic anhydride, both of which are formed by a " mixed " reaction, and concluded that reaction was preceded by anhydride formation. We found β-phenylpropiolyl chloride and β-2-naphthylpropiolic acid in benzene to give 4-phenylphenanthrene- (XI) and 1-2′-naphthylnaphthalene-2 : 3-dicarboxylic anhydride (XIV). The latter, which was isolated in very small quantity, was characterised by decarboxylation to 1 : 2′-dinaphthyl. Further, on cyclisation with anhydrous aluminium chloride in nitrobenzene the anhydride gave 9-oxo-3 : 4-7 : 8-dibenzofluorene-1-carboxylic acid (XV; R = CO_2H), which was



(XI) (XII) (XIII)

(XIV) (XV)

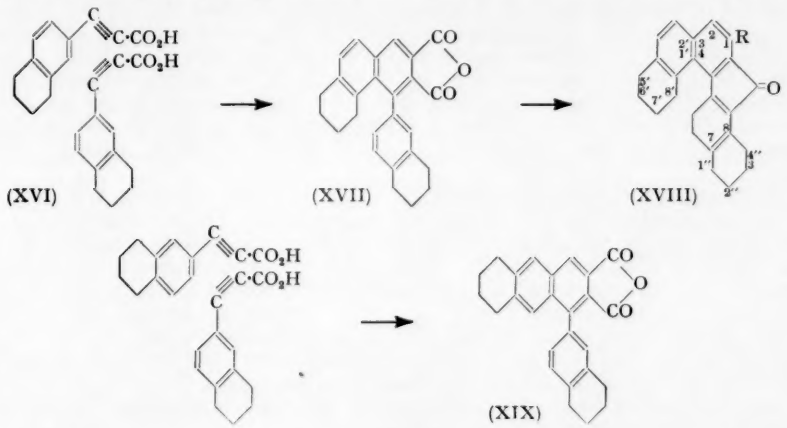
decarboxylated with copper bronze in quinoline to 1 : 2-5 : 6-dibenzofluorenone (XV; R = H) previously prepared by Badger (*J.*, 1941, 535) and by Swain and Todd (*J.*, 1941, 674).

Decarboxylation of 4-phenylphenanthrene-2 : 3-dicarboxylic anhydride by subliming the derived potassium salt from soda-lime and copper powder gave a low yield of 4-phenylphenanthrene and also 1 : 2-benzopyrene (XIII) formed by simultaneous cyclodehydro-

genation. The 4-phenylphenanthrene isolated in this reaction failed to give derivatives with picric acid and 1 : 3 : 5-trinitrobenzene, but it had properties identical with a sample prepared by dehydration and dehydrogenation of the product obtained by treating phenyllithium with 1 : 2 : 3 : 4-tetrahydro-4-oxophenanthrene. It is interesting that although phenylmagnesium bromide and 1 : 2 : 3 : 4-tetrahydro-1-oxophenanthrene readily give 1 : 2 : 3 : 4-tetrahydro-1-hydroxy-1-phenylphenanthrene (Bachmann and Wilds, *J. Amer. Chem. Soc.*, 1938, **60**, 624), in a similar reaction with 1 : 2 : 3 : 4-tetrahydro-4-oxophenanthrene only the reduction product, 1 : 2 : 3 : 4-tetrahydro-4-hydroxyphenanthrene, was isolated (Cook, Hewett, and Hieger, *J.*, 1933, 398).

The absorption spectrum of 4-phenylphenanthrene (Fig. 2*C*) shows predominantly the phenanthrene structure and resembles closely that of 4-2′-naphthylphenanthrene. Cyclisation of 4-phenylphenanthrene-2 : 3-dicarboxylic anhydride gave 9-oxonaphtho(2′ : 1′-3 : 4)fluorene-1-carboxylic acid (XII; R = CO_2H) which was decarboxylated to naphtho(2′-1′-3 : 4)fluorenone (XII; R = H).

Dimerisation of β-(5 : 6 : 7 : 8-tetrahydro-2-naphthyl)propiolic acid (XVI) with acetic anhydride gave a mixture of two isomeric anhydrides which were difficult to separate. Fractional crystallisation gave 5 : 6 : 7 : 8-tetrahydro-4-(5 : 6 : 7 : 8-tetrahydro-2-naphthyl)-phenanthrene-2 : 3-dicarboxylic anhydride (XVII), which was present in the greater quantity. It was characterised by dehydrogenation with palladium–charcoal to 4-2′-naphthylphenanthrene-2 : 3-dicarboxylic anhydride identical with the anhydride prepared by the dimerisation of β-2-naphthylpropiolic acid; and dehydrogenation and decarboxylation of the derived sodium salt of the anhydride (XVII) gave naphtho(2′ : 3′-1 : 2)pyrene. Also cyclisation of the anhydride gave the acid (XVIII; R = CO_2H), which was decarboxylated and dehydrogenated to give the red 7 : 8-benzonaphtho(2′ : 1′-3 : 4)fluorenone (V; R = H) identical with that previously obtained. The combined mother-liquors from



the recrystallisation of the anhydride (XVII) yielded more of this anhydride and also some of the isomer (XIX). The sodium salt from this anhydride was dehydrogenated and decarboxylated with copper powder and palladium–charcoal to 1-2′-naphthylanthracene. The absorption spectrum of 1-2′-naphthylanthracene (Fig. 3*A*) shows absorption bands for both anthracene and naphthalene and resembles that of 9 : 10-di-1′-naphthylanthracene (Jones, *J. Amer. Chem. Soc.*, 1941, **63**, 1658).

Experimental

1-1′-*Naphthylphenanthrene*-2 : 3-*dicarboxylic Anhydride* (I).—After being refluxed for 2 hr., a solution of β-1-naphthylpropiolic acid (5 g.) in acetic anhydride (20 c.c.) was concentrated to half its volume, and glacial acetic acid (10 c.c.) was added. After cooling, the anhydride (3·8 g.) separated as fine needles, m. p. 232° (from glacial acetic acid) (Found : C, 83·6; H, 3·9. Calc.

for $C_{26}H_{14}O_3$: C, 83·4; H, 3·7%). West (*loc. cit.*) gives m. p. 207—209°. Wojack *et al.* (*loc. cit.*) give m. p. 206°.

2 : 3-*Benzoperylene* (III).—1-1′-Naphthylphenanthrene-2 : 3-dicarboxylic anhydride (4·5 g.) was dissolved in methyl-alcoholic potassium hydroxide (6 c.c. of a 25% solution) and the solution was evaporated to dryness on a water-bath. An intimate mixture of this potassium salt, powdered soda-lime (10 g.), and copper powder (4 g.) was heated in a test-tube, gradually at first, inside a Pyrex glass tube at 0·2 mm. in the presence of a slow stream of carbon dioxide. Even distribution of heat was obtained by using a T burner and a copper tube to surround the heated portion of the Pyrex tube. When no further sublimate condensed on the walls of the Pyrex tube, heating was stopped and the semi-solid sublimate was taken up in hot benzene–ethanol and treated with 1 : 3 : 5-trinitrobenzene (4·0 g.) in ethanol. Fine red-brown needles of the *trinitrobenzene* complex of 2 : 3-benzoperylene (0·6 g.) separated on cooling; this had m. p. 208—209° (from ethanol) (Found: C, 70·1; H, 3·5. $C_{30}H_{17}O_6N_3$ requires C, 69·9; H, 3·3%). The filtrate after concentration and treatment with charcoal deposited yellow crystals (2·2 g.) of the *trinitrobenzene* complex of 1-1′-naphthylphenanthrene, m. p. 152—153° (from ethanol) (Found: N, 8·3. $C_{30}H_{19}O_6N_3$ requires N, 8·1%). The latter complex (1·8 g.) was decomposed by stannous chloride (8·0 g.) in boiling 50% aqueous ethanol (40 c.c.) containing concentrated hydrochloric acid (30 c.c.), to give a white precipitate of 1-1′-naphthylphenanthrene (0·8 g.), m. p. 115° (from ethanol). It gave an orange picrate, m. p. 135°. Bachmann and Deno (*loc. cit.*) give m. p. 115—116° and picrate, m. p. 135—136°. The trinitrobenzene complex of 2 : 3-benzoperylene was similarly decomposed and gave 2 : 3-*benzoperylene* as deep yellow plates, m. p. 200—201° (from benzene or ethanol) after chromatography in benzene on alumina (Found: C, 95·6; H, 4·7. $C_{24}H_{14}$ requires C, 95·4; H, 4·6%). It gave a blue fluorescence in ethanol.

1-1′-Naphthylphenanthrene (0·2 g.) was refluxed for 1 hr. with copper bronze (0·2 g.). The resulting oil was taken up in hot benzene–ethanol and after addition of 1 : 3 : 5-trinitrobenzene a small quantity of the red-brown complex with 2 : 3-benzoperylene separated, on cooling, as needles, m. p. 207°.

9-*Oxo*-5 : 6-*benzonaphtho*(1′ : 2′-3 : 4)*fluorene*-1-*carboxylic Acid* (II; R = CO_2H).—1-1′-Naphthylphenanthrene-2 : 3-dicarboxylic anhydride (2·5 g.) was dissolved in nitrobenzene (30 c.c.) and cooled to 0°; anhydrous aluminium chloride (4 g.) was then added during 10 min. with cooling. After 4 hr. at room temperature and 10 min. at 50° the mixture was poured on ice and hydrochloric acid. The residue remaining after steam-distillation was broken up, filtered off, and recrystallised from a large volume of xylene–acetic acid, to give the *acid* as brown-grey needles (2·1 g.), m. p. 333—335° (Found: C, 83·1; H, 4·0. $C_{26}H_{14}O_3$ requires C, 83·4; H, 3·7%).

5 : 6-*Benzonaphtho*(1′-2′-3 : 4)*fluorenone* (II; R = H).—The foregoing acid (1·3 g.) was heated on an oil-bath at 200—210° for 2 hr. with copper powder (1 g.) in quinoline (15 c.c.). The cooled, filtered solution was poured into dilute hydrochloric acid, and the precipitate was filtered off and taken up in benzene (charcoal). Bright brick-red clusters of fine needles of 5 : 6-*benzonaphtho*(1′ : 2′-3 : 4)*fluorenone* (0·7 g.) which separated on cooling had m. p. 245° (Found: C, 90·6; H, 4·5. $C_{25}H_{14}O$ requires C, 90·9; H, 4·3%). This readily gave an *oxime*, m. p. 260—261°, as clusters of fine orange needles from aqueous ethanol (Found: N, 4·0. $C_{25}H_{15}ON$ requires N, 4·1%). The fluorenone (50 mg.) was heated to 300—310° for 10 min. with potassium hydroxide (0·5 g.), and the cooled melt was dissolved in water and acidified, to give an acid which was decarboxylated to 1-1′-naphthylphenanthrene (identified as the trinitrobenzene complex, m. p. 152°) by copper bronze in boiling quinoline.

αβ-*Dibromo*-β-2-*naphthylpropionic Acid*.—β-2-Naphthylacrylic acid (4·5 g.), suspended in carbon tetrachloride (50 c.c.), was treated during 15 min. with a slight excess of bromine (3·8 g.) in carbon tetrachloride (20 c.c.) in the presence of strong artificial light. Then the suspension was stirred occasionally for 1 hr. and next concentrated almost to dryness in a current of air at room temperature. The precipitate was filtered off and washed with carbon tetrachloride. Recrystallisation from chloroform gave the *dibromo-acid* (6·5 g.) as fine white needles, m. p. 188° (decomp.) (Found: C, 43·7; H, 3·0. $C_{13}H_{10}O_2Br_2$ requires C, 43·6; H, 2·8%).

β-2-*Naphthylpropiolic Acid*.—αβ-Dibromo-β-2-naphthylpropionic acid (34 g.) was dissolved in methanol (50 c.c.), and heated with potassium hydroxide in methanol (100 c.c. of 25% solution) on a steam-bath. After evaporation to dryness the solid residue was taken up in methanol (50 c.c.) and again evaporated to dryness. The residue was then dissolved in water, chilled, and acidified. The precipitated *acid* was recrystallised from carbon tetrachloride as white needles (19·5 g.), m. p. 143—144° with previous softening (Found: C, 79·4; H, 4·3. $C_{13}H_8O_2$ requires C, 79·6; H, 4·1%).

4-2′-*Naphthylphenanthrene*-2 : 3-*dicarboxylic Anhydride* (IV).—β-2-Naphthylpropiolic acid (15 g.) was refluxed for 1 hr. with acetic anhydride (60 c.c.); acetic acid (30 c.c.) was then added. The precipitate which formed on cooling was recrystallised from a large volume of acetic acid (charcoal), to give the *anhydride* (11 g.), m. p. 265° (Found: C, 83·0; H, 4·1. $C_{26}H_{14}O_3$ requires C, 83·4; H, 3·7%).

Decarboxylation of 4-2′-*Naphthylphenanthrene*-2 : 3-*dicarboxylic Anhydride* (IV).—A mixture of 4-2′-naphthylphenanthrene-2 : 3-dicarboxylic anhydride (10 g.), powdered soda-lime (25 g.), and copper powder (5 g.) was heated at 0·2 mm. in the presence of carbon dioxide until no further sublimate condensed. The sublimate was taken up in benzene, concentrated, and chromatographed on alumina to give three fractions. The first was concentrated to give white needles of 4-2′-*naphthylphenanthrene* (3·0 g.), m. p. 105—106° (from ethanol) (Found: C, 94·4; H, 5·6. $C_{24}H_{16}$ requires C, 94·7; H, 5·3%). The second fraction yielded clusters of red needles of 7 : 8-*benzonaphtho*(2′ : 1′-3 : 4)*fluorenone* (V; R = H) (0·45 g.), m. p. 239° from benzene (Found: C, 90·9, 90·7; H, 4·6, 4·3. $C_{25}H_{14}O$ requires C, 90·9; H, 4·2%) [*oxime*, m. p. 230—231°, orange needles from ethanol (Found: N, 4·0. $C_{25}H_{15}ON$ requires N, 4·1%)]. The third fraction, 6 : 7-*benzonaphtho*(2′ : 1′-3 : 4)*fluorenone* (VII) (0·95 g.), m. p. 203—204°, lemon-yellow needles from benzene (Found: C, 91·0; H, 4·6%), gave an *oxime*, m. p. 265°, as yellow needles from ethanol (Found: N, 4·0%), and a 2 : 4-*dinitrophenylhydrazone*, m. p. 321—323°, as red needles from ethanol (Found: N, 10·9. $C_{31}H_{18}O_4N_4$ requires N, 11·0%).

7 : 8-Benzonaphtho(2′ : 1′-3 : 4)fluorenone (0·2 g.) was heated at 280—300° for ½ hr. with potassium hydroxide (1·0 g.). The crude potassium salt which floated on the melt was removed, ground with copper powder (0·2 g.), and sublimed at 0·2 mm./360°, to give naphtho(2′ : 3′-1 : 2)-pyrene (VI), m. p. and mixed m. p. 259—260° (from benzene) [picrate, red-brown needles (from benzene), m. p. 213°]. Clar (*J.*, 1949, 2168) gives hydrocarbon, m. p. 259—260°, and picrate, m. p. 212—213°. 6 : 7-Benzonaphtho(2′ : 1′-3 : 4)fluorenone also gave naphtho(2′ : 3′-1 : 2)-pyrene when similarly treated.

7 : 8-Benzonaphtho(2′ : 1′-3 : 4)fluorenone (0·15 g.) was heated at 280—300° for ½ hr. with potassium hydroxide (1·0 g.), and the cooled melt was dissolved in warm water and acidified with dilute hydrochloric acid. The liberated acid was filtered off, dried, and heated for 2 hr. with copper bronze (0·2 g.) in quinoline (4 c.c.) at 210—220°. The product was worked up as previously described, to give 4-2′-naphthylphenanthrene m. p. 105—106° (from ethanol), after purification by chromatography on alumina. The same hydrocarbon was obtained when 6 : 7-benzonaphtho(2′ : 1′-3 : 4)fluorenone was similarly treated.

7 : 8-*Benzonaphtho*(2′ : 1′-3 : 4)*fluorene*.—7 : 8-Benzonaphtho(2′ : 1′-3 : 4)fluorenone (0·28 g.) was heated at 200—210° for 6 hr. in a sealed tube with 85% hydrazine hydrate (0·6 c.c.). The solid product was taken up in benzene, chromatographed on alumina, and crystallised from ethanol–benzene, to give the *fluorene* (0·21 g.) as flat needles, m. p. 138—139° (Found: C, 95·0; H, 5·2. $C_{25}H_{16}$ requires C, 94·9; H, 5·1%). It gave a *dipicrate*, red-brown needles, m. p. 175—176° (Found: N, 10·8. $C_{37}H_{22}O_{14}N_6$ requires N, 10·9%).

6 : 7-*Benzonaphtho*(2′ : 1′-3 : 4)*fluorene*.—6 : 7-Benzonaphtho(2′ : 1′-3 : 4)fluorenone (0·12 g.) was reduced by hydrazine hydrate (0·3 c.c.) as just described. After chromatography in benzene on alumina the *fluorene* (80 mg.) was obtained as long white needles, m. p. 182—183° (Found: C, 94·5; H, 5·4. $C_{25}H_{16}$ requires C, 94·9; H, 5·1%). It gave a brick-red *dipicrate*, m. p. 176° (Found: N, 10·6%), which depressed the melting point of the previous dipicrate.

9-*Oxo*-7 : 8-*benzonaphtho*(2′ : 1′-3 : 4)*fluorene*-1-*carboxylic Acid* (V; R = CO_2H).—(*a*) 4-2′-Naphthylphenanthrene-2 : 3-dicarboxylic anhydride (30 g.) was set aside for 3 days with anhydrous hydrogen fluoride (approx. 40 c.c.). The brown solid remaining after the hydrogen fluoride had evaporated was insoluble in alkali. It was recrystallised from a large volume of acetic acid (charcoal), to give the *acid* (2·5 g.) as fibrous grey-brown needles, m. p. 295—296° (Found: C, 82·8; H, 4·2. $C_{26}H_{14}O_3$ requires C, 83·4; H, 3·7%).

(*b*) 4-2′-Naphthylphenanthrene-2 : 3-dicarboxylic anhydride (1·8 g.) in nitrobenzene (20 c.c.) was treated with anhydrous aluminium chloride (1·4 g.) at room temperature, warmed at 50—60° for 2 hr., and poured into dilute hydrochloric acid. After removal of the nitrobenzene in steam the residue recrystallised from acetic acid, to give the acid (1·2 g.), m. p. 294—296°.

7 : 8-*Benzonaphtho*(2′ : 1′-3 : 4)*fluorenone* (V; R = H).—The above acid (0·2 g.) was heated for 1½ hr. with copper powder (0·2 g.) in quinoline (3 c.c.). The filtered, cooled solution was poured into dilute hydrochloric acid, and the solid filtered off and recrystallised from benzene (charcoal), to give 7 : 8-benzonaphtho(2′ : 1′-3 : 4) fluorenone (0·11 g.), m. p. 238—239° undepressed on mixing with the previous sample.

9-*Hydroxy*-7 : 8-*benzonaphtho*(2′ : 1′-3 : 4)*fluorene*.—7 : 8-Benzonaphtho(2′ : 1′-3 : 4)fluoren-

one (0·25 g.) was heated at 100° for 3 hr. with zinc dust (5 g.) in acetic acid (30 c.c.). The solution was filtered and poured into water, and the white solid was filtered off and recrystallised from ethanol (charcoal), to give the *hydroxyfluorene* (0·18 g.) as colourless needles, m. p. 207° (Found: C, 89·8; H, 5·0. $C_{25}H_{16}O$ requires C, 90·3; H, 4·8%). When distilled from zinc dust this gave 7 : 8-benzonaphtho(2′ : 1′-3 : 4)fluorene, m. p. 138—139° after chromatography in benzene on alumina.

Naphtho(2′ : 3′-1 : 2)*pyrene* (VI).—4-2′-Naphthylphenanthrene (0·3 g.) was added at once and stirred into a melt of anhydrous aluminium chloride (2·5 g.) and sodium chloride (0·5 g.) at 120°. The mixture was allowed to cool to 90° during 5 min. Ice and hydrochloric acid were added and the solid was filtered off, taken up in benzene, dried, and chromatographed on alumina, to give naphtho(2′ : 3′-1 : 2)pyrene, m. p. and mixed m. p. 258—259°.

αβ-*Dibromo*-β-9-*phenanthrylpropionic Acid*.—β-9-Phenanthrylacrylic acid (Bachmann and Kloetzel, *J. Amer. Chem. Soc.*, 1937, **59**, 2207) (6·5 g.) was suspended in chloroform (30 c.c.), and bromine (3 g.) in carbon tetrachloride (20 c.c.) was added (10 min.) with stirring in the presence of bright artificial light at room temperature. After 2 hr. the solution was evaporated to approx. 20 c.c. in a current of air, and the *dibromo-acid* was filtered off, washed with carbon tetrachloride, and recrystallised from acetic acid, to give white needles (4·3 g.), m. p. 206—207° (decomp.) (Found: C, 50·5; H, 3·2. $C_{17}H_{12}O_2Br_2$ requires C, 50·1; H, 2·9%).

β-9-*Phenanthrylpropiolic Acid* (VIII).—The above dibromo-acid (4·2 g.), suspended in methanol (20 c.c.), was treated with potassium hydroxide in methanol (30 c.c. of a 20% solution), and the whole was evaporated to dryness on a steam-bath. The evaporation was repeated twice after the addition of further methanol (50 c.c.), and the residue was then taken up in water, chilled, and acidified, to give β-9-*phenanthrylpropiolic acid* (2·4 g.), m. p. 182—183° (Found: C, 82·5; H, 3·6. $C_{17}H_{10}O_2$ requires C, 82·9; H, 4·1%).

1-9′-*Phenanthryltriphenylene*-2 : 3-*dicarboxylic Anhydride* (IX).—β-9-Phenanthrylpropiolic acid (2·2 g.) was refluxed for 2 hr. with acetic anhydride (20 c.c.), concentrated to 10 c.c., and poured into glacial acetic acid (10 c.c.). The crystalline solid which separated on cooling was recrystallised from acetic acid, to give the *anhydride* (1·8 g.) as pale lemon-yellow crystals, m. p. 325—327° (Found: C, 86·3; H, 4·1. $C_{34}H_{18}O_3$ requires C, 86·1; H, 3·8%).

1 : 2-3 : 4-5 : 5a : 6-11 : 11a : 12-*Tetrabenzonaphthacene* (X).—(*a*) 1-9′-Phenanthryltriphenylene-2 : 3-dicarboxylic anhydride (0·8 g.) was taken up in methanol (20 c.c.) containing sodium hydroxide (0·5 g.), and the solution was evaporated to dryness. This sodium salt was mixed with powdered soda-lime (6 g.) and copper powder (5 g.) and heated in the presence of carbon dioxide at 0·3 mm. until decarboxylation and sublimation were complete. The sublimate was chromatographed in benzene on alumina and eluted with benzene. The first fraction, recrystallised from benzene–ethanol, gave colourless clusters of needles of 1-9′-*phenanthryltriphenylene* (0·15 g.), m. p. 216—217° (Found: C, 94·8; H, 5·0. $C_{32}H_{20}$ requires C, 95·0; H, 5·0%). With 2 mols. of 1 : 3 : 5-trinitrobenzene it gave a *derivative*, m. p. 178°, as yellow needles from ethanol (Found: N, 10·3. $C_{44}H_{26}O_{12}N_6$ requires N, 10·1%). 1 : 2-3 : 4-5 : 5a - 6-11 : 11a : 12-*Tetrabenzonaphthacene* (30 mg.) was eluted from the column by a large volume of benzene and recrystallised from xylene as pale yellow needles m. p. 289—290° (Found: C, 95·4; H, 4·5. $C_{32}H_{18}$ requires C, 95·5; H, 4·5%).

(*b*) 1-9′-Phenanthryltriphenylene (70 mg.) was heated at 400° for 3 hr. with 10% palladium–charcoal (40 mg.). The resulting product was chromatographed in benzene on alumina, to give 1 : 2-3 : 4-5 : 5*a* : 6-11 : 11*a* : 12-tetrabenzonaphthacene, m. p. 289—290°, preceded by a small quantity of unchanged starting material.

Interaction of Phenylpropiolic Acid and β-2-*Naphthylpropiolic Acid*.—β-2-Naphthylpropiolic acid (3·0 g.) and β-phenylpropiolic acid (4·5 g.) were each dissolved in acetic acid (25 c.c.) and then mixed. Acetic anhydride (30 c.c.) was added and the resulting solution was refluxed for 2 hr. and concentrated to approx. 20 c.c. The crystalline product precipitated on cooling was recrystallised from a large volume of glacial acetic acid, to give 4-*phenylphenanthrene*-2 : 3-*dicarboxylic anhydride* (XI) (0·6 g.), m. p. 283°, as flat needles (Found: C, 81·4; H, 3·5. $C_{22}H_{12}O_3$ requires C, 81·5; H, 3·7%). The solid which separated on further concentration of the mother liquors was recrystallised, to give 1-phenylnaphthalene-2 : 3-dicarboxylic anhydride (2·4 g.), m. p. 252° (Baddar, *J.*, 1948, 1267, gives m. p. 252—253°) (Found: C, 78·4; H, 3·9. Calc. for $C_{18}H_{10}O_3$: C, 78·8; H, 3·7%), and 4-2′-naphthylphenanthrene-2 : 3-dicarboxylic anhydride (0·4 g.), m. p. 265°.

Reaction of β-*Phenylpropiolyl Chloride with* β-2-*Naphthylpropiolic Acid*.—β-Phenylpropiolyl chloride (4·5 g.) and β-2-naphthylpropiolic acid (6·0 g.) were refluxed for 48 hr. in benzene (60 c.c.). After a further 48 hr., at room temperature, the crystalline precipitate was filtered

off and recrystallised from acetic acid, to give 4-phenylphenanthrene-2 : 3-dicarboxylic anhydride (XI) (2·5 g.), m. p. 283°. Concentration of the acetic acid mother-liquors gave 1-2′-*naphthylnaphthalene*-2 : 3-*dicarboxylic anhydride* (XIV) which recrystallised from benzene as needles (0·12 g.), m. p. 218° (Found : C, 81·1; H, 3·9. $C_{22}H_{12}O_3$ requires C, 81·5; H, 3·7%). The anhydride (*ca.* 50 mg.) was heated at 210—220° for 2 hr. with copper bronze (0·1 g.) in quinoline (2 c.c.). The product was worked up in the usual manner, chromatographed in benzene on alumina, and treated with an excess of picric acid in ethanol, to give the picrate of 1 : 2′-dinaphthyl as orange needles, m. p. 123—124°. A solution of the picrate in benzene was passed down a column of alumina to give the hydrocarbon, m. p. 72—73°. Hooker and Fieser (*J. Amer. Chem. Soc.*, 1936, **58**, 1216) give m. p. of 1 : 2′-dinaphthyl as 74·5—75° and of picrate as 127—127·5° (corr.).

1 : 2-*Benzopyrene* (XIII) *and* 4-*Phenylphenanthrene*.—The dry potassium salt prepared from 4-phenylphenanthrene-2 : 3-dicarboxylic anhydride (1·0 g.) was decarboxylated by heat at 0·2 mm. with copper powder (2 g.) and soda-lime (5·0 g.) in nitrogen. The sublimate was taken up in benzene and chromatographed on alumina to give, in the first fraction, 4-phenylphenanthrene (40 mg.), m. p. 80—81° (white crystals from ethanol) undepressed on admixture with a specimen prepared from 1 : 2 : 3 : 4-tetrahydro-4-oxophenanthrene. The second fraction (pale yellow), after concentration, gave 1 : 2-benzopyrene (0·11 g.) very pale yellow plates, m. p. and mixed m. p. 175° (from benzene); this gave red-brown needles of the picrate, m. p. 226°, from ethanol. Cook and Hewett (*J.*, 1933, 395) give hydrocarbon, m. p. 178°, and picrate, m. p. 229—230°; the complex with 1 : 3 : 5-*trinitrobenzene* crystallised from ethanol as orange needles, m. p. 253—254° (Found : N, 9·1. $C_{26}H_{15}O_6N_3$ requires N, 9·0%).

9-*Oxonaphtho*(2′ : 1′-3 : 4)*fluorene*-1-*carboxylic Acid* (XII; R = CO_2H).—4-Phenylphenanthrene-2 : 3-dicarboxylic anhydride (0·15 g.) in nitrobenzene (5 c.c.) was treated with anhydrous aluminium chloride (0·12 g.) and warmed at 50° for 0·5 hr. The dark red solid obtained by working up in the usual manner crystallised from acetic acid, to give 9-*oxonaphtho*(2′ : 1′-3 : 4)-*fluorene*-1-*carboxylic acid* (0·11 g.), m. p. 240° (Found : C, 81·4; H, 3·9. $C_{22}H_{12}O_3$ requires C, 81·5; H, 3·7%).

Naphtho(2′ : 1′-3 : 4)*fluorenone* (XII; R = H).—The above acid (*ca.* 80 mg.) was decarboxylated at 210° for 0·5 hr. with copper bronze (0·1 g.) in quinoline (1 c.c.). This gave *naphtho*-(2′ : 1′-3 : 4)*fluorenone* (*ca.* 20 mg.), m. p. 148—149°, orange needles from ethanol (charcoal) (Found : C, 89·5; H, 4·3. $C_{21}H_{12}O$ requires C, 90·0; H, 4·3%).

9-*Oxo*-3 : 4-7 : 8-*dibenzofluorene*-1-*carboxylic Acid* (XV; R = CO_2H).—1-2′-Naphthylnaphthalene-2 : 3-dicarboxylic anhydride (0·1 g.) in nitrobenzene (5 c.c.) was heated with anhydrous aluminium chloride (0·1 g.) at 50° for 2 hr., giving the *acid* (90 mg.), m. p. 260—261° (brown needles from benzene) (Found : C, 81·0; H, 3·7. $C_{22}H_{12}O_3$ requires C, 81·5; H, 3·7%). The acid, with copper bronze in quinoline at 210° (3 hr.), gave, after sublimation of the product from soda-lime, 1 : 2-5 : 6-dibenzofluorenone, m. p. 164°, red cubes (from ethyl acetate). Badger (*J.*, 1941, 535) gives m. p. 164°.

1 : 2 : 3 : 4-*Tetrahydro*-4-*hydroxy*-4-*phenylphenanthrene*.—Bromobenzene (3·0 g.) in dry ether (30 c.c.) was treated with lithium (0·25 g.) with rapid stirring for 1 hr., most of the lithium reacting. 1 : 2 : 3 : 4-Tetrahydro-4-oxophenanthrene (2·5 g.) in ether (10 c.c.) was added dropwise and the mixture stirred for 3 hr. during which a complex settled out. The ether solution was decanted, and the solid was washed with dilute hydrochloric acid, filtered off, and recrystallised from benzene–light petroleum, to give 1 : 2 : 3 : 4-*tetrahydro*-4-*hydroxy*-4-*phenylphenanthrene* (1·6 g.) as large cubes, m. p. 108—109° (Found : C, 87·5; H, 6·4. $C_{20}H_{18}O$ requires C, 87·6; H, 6·6%).

1 : 2-*Dihydro*-4-*phenylphenanthrene*.—The above hydroxy-compound (1·2 g.) was distilled (b. p. 240—245°/20 mm.), to give 1 : 2-*dihydro*-4-*phenylphenanthrene* (1·0 g.) as a thick syrup which slowly crystallised. Recrystallisation from ethanol gave the hydrocarbon as colourless needles, m. p. 99—100° (Found : C, 93·4; H, 6·3. $C_{20}H_{16}$ requires C, 93·7; H, 6·3%).

4-*Phenylphenanthrene*.—The dihydro-compound (0·5 g.) was refluxed at 300—310° for 1 hr. with 5% palladium–charcoal (0·3 g.). Chromatography in benzene on alumina gave 4-*phenylphenanthrene* (0·25 g.) as colourless rods, m. p. 81° (Found : C, 94·1; H, 5·5. $C_{20}H_{14}$ requires C, 94·5; H, 5·5%), together with 1 : 2-benzopyrene isolated as the trinitrobenzene derivative (*ca.* 20 mg.; m. p. 252—253°).

6-1′-*Chlorovinyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*.—Phosphorus pentachloride (134 g.) and 6-acetyl-1 : 2 : 3 : 4-tetrahydronaphthalene (110 g.) were heated at 70° for 15 min. Fractionation under reduced pressure gave phsophorus oxychloride and then the *chloroethylene* (70 g.), b. p. 130—135°/16 mm. (Found : C, 75·2; H, 6·4. $C_{12}H_{13}Cl$ requires C, 74·8; H, 6·7%).

6-*Ethynyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*.—The above chloroethylene (69 g.) was refluxed on a water-bath for 5 hr. with potassium hydroxide (50 g.) in ethanol (100 c.c.). The solution was poured into ice-water, and the oil which separated was extracted with ether and distilled, to give the *acetylene* (33 g.), b. p. 110—112°/2 mm. (Found : C, 92·5; H, 7·7. $C_{12}H_{12}$ requires C, 92·3; H, 7·7%).

β-(5 : 6 : 7 : 8-*Tetrahydro*-2-*naphthyl*)*propiolic Acid* (XVI).—6-Ethynyl-1 : 2 : 3 : 4-tetrahydronaphthalene (12 g.) in dry ether (50 c.c.) was added dropwise to a Grignard reagent prepared from magnesium (3 g.), ethyl bromide (14 g.), and ether (50 c.c.). After 3 hours' refluxing the mixture was poured on a large excess of solid carbon dioxide and left for 8 hr. Cold dilute hydrochloric acid was added and the ether layer separated and extracted with dilute sodium hydroxide. Acidification of the cold alkaline extracts gave the acetylenic *acid* (8 g.), m. p. 114—115° (from carbon tetrachloride; slight orange colour) (Found : C, 78·2; H, 6·6. $C_{13}H_{12}O_2$ requires C, 78·0; H, 6·0%).

Dimerisation of β-(5 : 6 : 7 : 8-*Tetrahydro*-2-*naphthyl*)*propiolic Acid*.—The above acid (6·0 g.) was refluxed for 2 hr. with acetic anhydride (30 c.c.) and after the addition of acetic acid (20 c.c.) and water (10 c.c.) the solution was concentrated to about 20 c.c. The solid which separated on cooling was recrystallised several times from glacial acetic acid and benzene–light petroleum, to give 5 : 6 : 7 : 8-*tetrahydro*-4-(5 : 6 : 7 : 8-*tetrahydro*-2-*naphthyl*)*phenanthrene*-2 : 3-*dicarboxylic anhydride* (XVII) (1·6 g.) as colourless flat needles, m. p. 204—205° (Found : C, 81·6; H, 6·0. $C_{26}H_{22}O_3$ requires C, 81·7; H, 5·8%). The combined mother-liquors were concentrated, benzene and light petroleum were added, and the solution was set aside for several days to crystallise slowly. Large pale green cubes crystallised among hard clusters of crystals. These were filtered off and separated by hand, and each recrystallised from acetic acid and benzene–light petroleum. 5 : 6 : 7 : 8-*Tetrahydro*-1-(5 : 6 : 7 : 8-*tetrahydro*-2-*naphthyl*)*anthracene*-2 : 3-*dicarboxylic anhydride* (XIX) (0·9 g.), m. p. 194—195° depressed on admixture with the previously isolated anhydride, was obtained from the pale green cubes as fine white needles (Found : C, 81·6; H, 5·5. $C_{26}H_{22}O_3$ requires C, 81·7; H, 5·8%). The hard clusters of crystals yielded a further quantity of the anhydride previously isolated (1·2 g.).

The anhydride (XVII) (0·2 g.) was heated at 320—340° for ½ hr. with 30% palladium–charcoal (50 mg.). Recrystallisation from acetic acid (charcoal) gave colourless needles of 4-2′-naphthylphenanthrene-2 : 3-dicarboxylic anhydride (IV), m. p. 264—265°, undepressed on admixture with that prepared by the dimerisation of β-2-naphthylpropiolic acid.

Naphtho(2′ : 3′-1 : 2)*pyrene* (VI).—5 : 6 : 7 : 8-Tetrahydro-4-(5 : 6 : 7 : 8-tetrahydro-2-naphthyl)phenanthrene-2 : 3-dicarboxylic anhydride (0·9 g.) was dissolved in dilute aqueous sodium hydroxide containing a little ethanol, and was concentrated until the sodium salt began to be precipitated. The semi-solid sodium salt which separated on cooling was washed by decantation, dried, and thoroughly mixed with 30% palladium–charcoal (0·1 g.) and copper powder (1·0 g.). After being heated at 320—360° for 4 hr. the mixture was dry-distilled and the condensate was chromatographed in benzene on alumina, to give naphtho(2′ : 3′-1: 2)pyrene (0·18 g.), m. p. and mixed m. p. 258—259°.

5′ : 6′ : 7′ : 8′-1″ : 2″ : 3″ : 4″-*Octahydro*-9-*oxo*-7 : 8-*benzonaphtho*(2′ : 1′-3 : 4)*fluorene*-1-*carboxylic Acid* (XVIII; R = CO_2H).—5 : 6 : 7 : 8-Tetrahydro-4-(5 : 6 : 7 : 8-tetrahydro-2-naphthyl)phenanthrene-2 : 3-dicarboxylic anhydride (0·2 g.) in nitrobenzene (10 c.c.) was treated with anhydrous aluminium chloride (0·3 g.). After 1 hr. at room temperature and ½ hr. at 50° the solution was poured into dilute hydrochloric acid and steam distilled, and the residue was recrystallised from benzene, to give the *keto-acid* (0·12 g.) as large red cubes, m. p. 273—274° (Found : C, 81·9; H, 6·0. $C_{26}H_{22}O_3$ requires C, 81·7; H, 5·8%). The keto-acid (*ca.* 70 mg.) was decarboxylated by copper bronze in quinoline for 1 hr. and the product dehydrogenated at 340—360° for 2 hr. with 30% palladium charcoal. This gave 7 : 8-benzonaphtho(2′ : 1′-3 : 4)-fluorenone (V; R = H), m. p. 238—239° (after chromatography in benzene on alumina), undepressed on admixture with the sample previously prepared.

1-2′-*Naphthylanthracene*.—The sodium salt prepared from 5 : 6 : 7 : 8-tetrahydro-1-(5 : 6 : 7 : 8-tetrahydro-2-naphthyl)anthracene-2 : 3-dicarboxylic anhydride (0·5 g.) by concentration in dilute aqueous sodium hydroxide containing ethanol was dehydrogenated by 30% palladium–charcoal (0·2 g.) and copper bronze (2·0 g.) for 3 hr. at 320—360°. The distillate which was formed on dry distillation was chromatographed in benzene on alumina, giving 1-2′-*naphthylanthracene* (30 mg.) as colourless plates from ethanol–benzene, m. p. 142—143° (Found : C, 94·5; H, 5·4. $C_{24}H_{16}$ requires C, 94·7; H, 5·3%). Its solutions had a purple fluorescence. It gave a brick-red 1 : 3 : 5-trinitrobenzene *complex*, m. p. 127—128° (from ethanol–benzene) (Found : N, 7·8. $C_{30}H_{19}O_6N_3$ requires N, 8·1%).

The author thanks Professor J. W. Cook for suggesting this investigation and for valuable discussions. He is grateful to the President and Council of the Chemical Society for the award of the Corday–Morgan Commonwealth Fellowship, to the Council of the University of Otago, New Zealand, for generous leave of absence, and to the Chemistry Department, University of Glasgow, for hospitality. He thanks Dr. E. Clar for specimens of certain hydrocarbons for mixed m. p. determinations and for discussions of ultra-violet spectra, Profesor R. A. Raphael for his interest, and Mr. J. M. L. Cameron and Miss M. W. Christie for microanalyses.

UNIVERSITY OF GLASGOW. [*Received, May 17th*, 1954.]

Synthetic Plant Hormones. Part II. Some Glucosides and Aldehydes.*

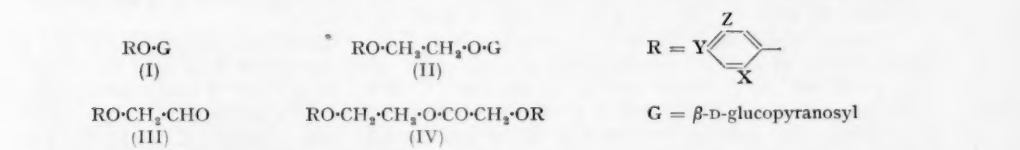
By (MISS) M. H. MAGUIRE and G. SHAW.

[Reprint Order No. 5450.]

Several chlorophenyl and chlorophenoxyethyl glucosides and chlorophenoxyacetaldehydes have been prepared in an attempt to obtain readily translocatable plant-growth inhibitors.

AN extension of the ideas described in Part I* for the preparation of readily translocatable plant-growth inhibitors has led us to prepare a series of chlorophenyl (I) and chlorophenoxyethyl β-D-glucosides (II) and chlorophenoxyacetaldehydes (III). Chlorophenoxyethyl tetra-*O*-acetyl-β-D-glucosides were prepared by the Koenigs–Knorr reaction (Helferich and Klein, *Annalen*, 1926, **450**, 219: Reynolds and Evans, *J. Amer. Chem. Soc.*, 1938, **60**, 2559) from tetra-*O*-acetyl-α-D-glucopyranosyl bromide with the appropriate chlorophenoxyethanol and silver oxide in dry chloroform. Chlorophenyl tetra-*O*-acetyl-β-D-glucosides were prepared by Helferich and Smitz-Hillebrecht's method (*Ber.*, 1933, **66**, 378) from the chlorophenol, penta-*O*-acetyl-β-D-glucose, and toluene-*p*-sulphonic acid. Catalytic deacetylation with sodium or barium methoxide ("Polarimetry, Saccharimetry and the Sugars," Circular C 440, Nat. Bur. Stand., U.S.A., 1942, p. 493) of the tetra-*O*-acetyl derivatives gave the required glucosides.

Several routes to the aldehydes (III) were investigated. Phenoxyacetaldehyde (III; R = Ph) has been prepared in small yield by the oxidation of 2-phenoxyethanol with chromic



acid (Halasz, *Bull. Soc. chim.*, 1941, **8**, 170); oxidation of (III; X = Y = Cl, Z = H) with this reagent gave no aldehyde but a moderate amount of the ester (IV; X = Y = Cl). A newer oxidant, *tert.*-butyl chromate (Oppenhauer and Oberrausch, *Anal. Asoc. Quím. Argentina*, 1949, **37**, 246) is claimed to oxidise primary alcohols to aldehydes exclusively, but with 2-*p*-chlorophenoxyethanol gave much tar and a small yield of the acid. Phenoxyacetaldehyde has also been synthesised, in unstated yield, by hydrolysis of its acetal obtained from chloroacetal and sodium phenoxide (Autenrieth, *Ber.*, 1891, **24**, 162); an attempt to duplicate this reaction but with sodium 2 : 4-dichlorophenoxide was unsuccessful. Hatch and Nesbitt (*J. Amer. Chem. Soc.*, 1945, **67**, 39) prepared phenoxyacetaldehyde in 45% yield by the oxidation of glycerol α-phenyl ether with lead tetra-acetate. This method was adopted by us and with minor modifications gave generally better yields than

* Part I, *J.*, 1953, 1479.

those claimed for the phenyl compound. The aldehydes readily polymerised at room temperature but formed water-soluble adducts with sodium hydrogen sulphite, and biological tests were carried out on these adducts. The aldehyde (III; X = Y = Cl, Z = H) formed a remarkably stable adduct with water which could be distilled *in vacuo* without dehydration.

In inhibition of germination tests, the glucosides and aldehyde-bisulphite compounds were compared with an equimolar amount of 2 : 4-dichlorophenoxyacetic acid (2 : 4-D) at a concentration equivalent to 5 lb. per acre by Mr. C. G. Greenham of the Division of Plant Industry, C.S.I.R.O., Canberra. The order of activity was 2 : 4-D or (III; X = Y = Cl, Z = H)>(II; X = Y = Cl, Z = H; or X = Z = H, Y = Cl) or (III; X = Z = H, Y = Cl; or X = Y = Z = Cl)>(II; X = Y = Z = Cl)>(I; X = Y = Z = Cl)>(inactive) (II; Y = Z = H, X = Cl) or (III; Y = Z = H, X = Cl) or (I; X = Y = Cl, Z = H; or X = Z = H, Y = Cl; or Y = Z = H, X = Cl). The results are similar to those obtained with aryl and aryloxyethyl phosphates (Part I, *loc. cit.*) and substantiate the suggestion that a *p*-chloro-group and a precursor of a phenoxyacetic acid are prerequisites for activity. Preliminary tests on mature skeleton weed (*Chondrilla juncea*) showed that, whereas all the more active compounds affected the aerial parts of the plant, only (III; X = Y = Cl, Z = H) had any significant effect on the root; the action of this compound is slow and its full effects have not, as yet, been assessed.

Experimental

[α] are for *c* = 2 in MeOH unless otherwise stated.

Aryloxyethyl Glucosides (II).—A solution of tetra-*O*-acetyl-β-D-glucopyranosyl bromide (Jeremias, Lucas, and MacKenzie, *J. Amer. Chem. Soc.*, 1948, **70**, 2598) (9 g.) in dry chloroform (60 ml.) was added with vigorous stirring during 45 min. to *p*-chlorophenoxyethanol (3·8 g.), iodine (0·3 g.), silver oxide (5·2 g.), " Drierite " (12 g.), and chloroform (250 ml.), and the mixture stirred for 9 hr., then filtered. The filtrate was evaporated, giving a viscous red residue (11·9 g.); this when crystallised from ethanol gave 2-p-*chlorophenoxyethyl tetra*-O-*acetyl*-β-D-*glucopyranoside* (3·1 g.) as colourless needles, m. p. 78°, $[\alpha]_D^{28}$ −20·5° (in $CHCl_3$) (Found: C, 52·45; H, 5·25. $C_{22}H_{27}O_{11}Cl$ requires C, 52·5; H, 5·45%). A solution of the acetate (3·05 g.) in anhydrous methanol (100 ml.) containing a small amount of sodium methoxide was kept overnight at 0°, then neutralised with methanolic acetic acid (phenolphthalein) and evaporated to a clear viscous gum; this was dissolved in boiling ethyl acetate, sodium acetate was filtered off, and the filtrate was evaporated. The residue crystallised when rubbed with dioxan and it recrystallised from dioxan–ether, to give 2-p-*chlorophenoxyethyl* β-D-*glucopyranoside hemihydrate* (dried *in vacuo*) (1·53 g.) as deliquescent needles, m. p. 52—53°, $[\alpha]_D^{17}$ −15·5° (*c*, 3·346) (Found: C, 49·0; H, 6·05. $C_{14}H_{19}O_7Cl,\frac{1}{2}H_2O$ requires C, 48·9; H, 5·85%).

Similar experiments led to 2-o-*chlorophenoxyethyl tetra*-O-*acetyl*-β-D-*glucopyranoside* (2·7 g. from 6·34 g. of alcohol), needles (from ethanol–water, after extraction with light petroleum), m. p. 63—64°, $[\alpha]_D^{28}$ −16·5° (in $CHCl_3$) (Found: C, 52·6; H, 5·3%); 2-o-*chlorophenoxyethyl* β-D-*glucopyranoside* (1·4 g. from 2 g. of acetate) was obtained as a brittle gum, $[\alpha]_D^{17\cdot5}$ −16·9° (*c*, 3·086), but analysis indicated it to be substantially pure (Found: C, 50·4; H, 5·95. $C_{14}H_{19}O_7Cl$ requires C, 50·23; H, 5·7%); 2-2′ : 4′-*dichlorophenoxyethyl tetra*-O-*acetyl*-β-D-*glucopyranoside* (6·26 g. from 7 g. of alcohol) separated from ethanol–water (after seeding with the *p*-chloro-analogue) as plates, m. p. 62—63°, $[\alpha]_D^{28}$ −14·5° (in $CHCl_3$) (Found: C, 49·25; H, 4·85. $C_{22}H_{26}O_{11}Cl_2$ requires C, 49·15; H, 4·9%), and 2-2′ : 4′-*dichlorophenoxyethyl* β-D-*glucopyranoside* (2 g. from 4 g. of acetate) as a brittle gum, $[\alpha]_D^{23}$ −16·6° (*c*, 2·77) (Found: C, 46·05; H, 5·1. $C_{14}H_{18}O_7Cl_2$ requires C, 45·5; H, 4·9); 2-2′ : 4′ : 5′-*trichlorophenoxyethyl tetra*-O-*acetyl*-β-D-*glucopyranoside* (48%) separated from ethanol–water as needles, m. p. 101—102°, $[\alpha]_D^{28}$ −15·0° (in $CHCl_3$) (Found: C, 45·9; H, 4·45. $C_{22}H_{25}O_{11}Cl_3$ requires C, 46·2; H, 4·4%), and 2-2′ : 4′ : 5′-trichlorophenoxyethyl β-D-glucopyranoside hydrate (as an *adduct* with dioxan) crystallised from dioxan–ether as needles, m. p. 57—60° (softening at 50°), $[\alpha]_D^{17\cdot5}$ −12·5° (*c*, 3·291) (Found: C, 42·25; H, 5·05. $C_{14}H_{17}O_7Cl_3,C_4H_8O_2,H_2O$ requires C, 42·4; H, 5·3%). The *anhydrous trichloroglucoside* was obtained when the adduct (0·1435 g.) was heated at 100°/1 mm. for 24 hr. to give, eventually, needles (0·1135 g. Calc. for loss of dioxan and water in the above molar proportions, 0·1136 g.), m. p. 118—119° (Found: C, 41·85; H, 4·35. $C_{14}H_{17}O_7Cl_3$ requires

C, 41·65; H, 4·25%); the anhydrous compound readily reverted to the adduct when rubbed with moist dioxan.

Aryl Glucosides (I).—Penta-*O*-acetyl-β-D-glucopyranose (20 g.), 2 : 4-dichlorophenol (33·5 g.), and toluene-*p*-sulphonic acid (0·3 g.) were heated together on a water-bath for 1½ hr., then cooled and treated with benzene (60 ml.), and the resultant solution was washed with water and 2N-sodium hydroxide until free from phenol, then dried and evaporated to a syrup (20 g.).

2 : 4-*Dichlorophenyl tetra*-O-*acetyl*-β-D-*glucopyranoside* (21%) separated from methanol as needles, m. p. 184—185°, $[\alpha]_D^{22}$ −40·5° (in $CHCl_3$) (Found: C, 48·95; H, 4·55. $C_{20}H_{22}O_{11}Cl_2$ requires C, 48·7; H, 4·5%). A solution of the acetate (4·36 g.) in methanol (300 ml.) containing a small amount of sodium methoxide was boiled under reflux for 15 min., then kept at room temperature for 24 hr. The solution was neutralised with methanolic acetic acid (phenolphthalein) and filtered, and the filtrate evaporated to give a crystalline residue; 2 : 4-*dichlorophenyl* β-D-*glucopyranoside* (4·3 g.) crystallised from propan-2-ol as needles, m. p. 173—174°, $[\alpha]_D^{20}$ −66° (Found: C, 44·15; H, 4·35. $C_{12}H_{14}O_6Cl_2$ requires C, 44·3; H, 4·35%).

Similarly 2 : 4 : 5-*trichlorophenyl tetra*-O-*acetyl*-β-D-*glucopyranoside* (8·1 g. from 30 g. of penta-*O*-acetyl-β-D-glucose) separated from methanol as needles, m. p. 175°, $[\alpha]_D^{24}$ −31° (in $CHCl_3$) (Found: C, 45·75; H, 4·0. $C_{20}H_{21}O_{10}Cl_3$ requires C, 45·5; H, 4·0%); 2 : 4 : 5-*trichlorophenyl* β-D-*glucopyranoside* (2·2 g. from 4·55 g. of acetate) separated from propan-2-ol as needles, m. p. 190—192°, $[\alpha]_D^{24\cdot5}$ −69° (Found: C, 39·7; H, 3·55. $C_{12}H_{13}O_6Cl_3$ requires C, 40·1; H, 3·65%); *p*-chlorophenyl tetra-*O*-acetyl-β-D-glucopyranoside (40%) crystallised from ethanol as needles, m. p. 124°, $[\alpha]_D^{24}$ −20° (in $CHCl_3$) (Found: C, 52·35; H, 5·05. Calc. for $C_{20}H_{23}O_{11}Cl$: C, 52·35; H, 4·95%) {(Dyfverman and Lindberg, *Acta Chem. Scand.*, 1950, **4**, 878, give m. p. 123—124°, $[\alpha]_D^{20}$ −20°}; *p*-chlorophenyl β-D-glucopyranoside (2·2 g. from 4·5 g. of acetate) crystallised from propan-1-ol as needles, m. p. 174—175°, $[\alpha]_D^{25}$ −65·5° (Found: C, 49·3; H, 5·35. Calc. for $C_{12}H_{15}O_6Cl$: C, 49·6; H, 5·2%) {(Dyfverman and Lindberg, *loc. cit.*, record m. p. 173—174°, $[\alpha]_D^{25}$ −69·5° (*c*, 1 in H_2O)}; *o*-chlorophenyl tetra-*O*-acetyl-β-D-glucopyranoside (20%) formed needles (from ethanol), m. p. 141—143°, $[\alpha]_D^{22}$ −46·5° (in $CHCl_3$) (Found: C, 52·55; H, 4·95%) {(Miller, *Contr. Boyce Thompson Inst.*, 1939, **11**, 25, records m. p. 150—151° (corr.), $[\alpha]_D^{23}$ −44·6° (*c*, 3·7559 in $CHCl_3$)}; *o*-chlorophenyl β-D-glucopyranoside (1·1 g. from 3·64 g. of acetate) crystallised from ethyl acetate–light petroleum as needles, m. p. 163—164°, $[\alpha]_D^{17\cdot5}$ −65·8° (*c*, 2·462) (Found: C, 49·9; H, 5·2%) {(Miller, *loc. cit.*, records m. p. 171—171·5° (corr.), $[\alpha]_D^{26}$ −65·3° (*c*, 3·579 in EtOH)}.

Aryloxyacetaldehydes (III).—(a) *Chromic acid oxidation.* To a solution of 2-2′ : 4′-dichlorophenoxyethanol (4 g.) in acetic acid (200 ml.) was added chromium trioxide (1·3 g.) slowly and with vigorous stirring; the solution was warmed to 50°, stirred for a further 15 min., then poured on ice; an oil separated and was extracted with ether, and the extract washed with sodium hydrogen carbonate solution and water, then dried and evaporated to an orange oil which crystallised; 2-2′ : 4′-*dichlorophenoxyethyl* 2 : 4-*dichlorophenoxyacetate* (IV; X = Y = Cl, Z = H) (2·7 g.) separated from ethanol as plates, m. p. 88—89° (Found: C, 46·9; H, 3·1. $C_{16}H_{12}O_4Cl_4$ requires C, 46·85; H, 2·95%); oxidation of 2-*p*-chlorophenoxyethanol with chromic acid under Halasz's conditions (*loc. cit.*) for 2-phenoxyethanol gave starting material and tar.

(b) tert.-*Butyl chromate.* Chromic oxide (30·8 g.) was added gradually to *tert.*-butyl alcohol (61·7 g.), and the red solution obtained was diluted with benzene (250 ml.); the solution was dried by vigorous shaking with sodium sulphate. To the filtered solution was added 2-*p*-chlorophenoxyethanol (21·6 g.) in benzene (170 ml.), and the solution set aside for 2 days. The excess of oxidant was decomposed by shaking the solution with aqueous oxalic and sulphuric acid and at this stage much tar was formed; evaporation of the dried solution and distillation of the residue *in vacuo* gave 2-*p*-chlorophenoxyethanol (3·9 g.) and a residue which crystallised from water as needles, m. p. 148°, not depressed when mixed with 2-*p*-chlorophenoxyacetic acid, m. p. 150°.

Oxidation of Glycerol Ethers with Lead Tetra-acetate.—The ethers were prepared by heating a mixture of the phenol, 3-chloropropane-1 : 2-diol and sodium hydroxide (Fairbourne and Stevens, *J.*, 1932, 1972). 3-2′ : 4′-*Dichlorophenoxypropane*-1 : 2-*diol* (74%) had b. p. 182—190°/3 mm. and crystallised from benzene–light petroleum as needles, m. p. 78—79° (Found: C, 45·8; H, 4·3. $C_9H_{10}O_3Cl_2$ requires C, 45·6; H, 4·25%). To a solution of 3-*p*-chlorophenoxypropane-1 : 2-diol (20·25 g.) in benzene (500 ml.) at 40—50° was added gradually and with vigorous stirring powdered lead tetra-acetate (44·32 g.); the mixture was kept at 50° for 1½ hr. and at 0° for 48 hr. The solution was filtered from lead acetate, washed with water, and again filtered to remove lead dioxide, then washed with sodium hydrogen carbonate solution (50 ml.; 5%) and water (2 × 50 ml.). Evaporation of the dried solvent gave a yellow viscous oil (15·5 g.); distillation of this gave p-*chlorophenoxyacetaldehyde* (12 g.) as a very pale yellow liquid,

b. p. 100—102°/2·5 mm. (Found : C, 56·35; H, 4·1. $C_8H_7O_2Cl$ requires C, 56·3; H, 4·15%); the *adduct* with sodium hydrogen sulphite separated from water as needles, m. p. 183° (Found : C, 35·1; H, 2·9. $C_8H_8O_5ClSNa$ requires C, 35·0; H, 2·95%), and the 2 : 4-*dinitrophenylhydrazone* from benzene–light petroleum as needles, m. p. 129—130° (Found : N, 16·05. $C_{14}H_{11}ON_4Cl$ requires N, 15·95%).

Similar experiments led to o-*chlorophenoxyacetaldehyde* (12·3 g. from 20·25 g. of ether), b. p. 104°/5 mm. (Found : C, 56·25; H, 4·2%), the sodium hydrogen sulphite *adduct hemihydrate*, needles (from water), m. p. 180° (Found : C, 33·85; H, 3·0. $C_8H_8O_5ClSNa,\frac{1}{2}H_2O$ requires C, 33·85; H, 3·2%), and the 2 : 4-*dinitrophenylhydrazone*, yellow needles (from ethanol), m. p. 153—154° (Found : N, 15·95%); 2 : 4-*dichlorophenoxyacetaldehyde hydrate* (13·3 g. from 23·7 g. of ether) had b. p. 120°/1·5 mm., m. p. 55—58° (Found : C, 43·36; H, 3·65. $C_8H_6O_2Cl_2,H_2O$ requires C, 43·05; H, 3·6%); the *adduct* with sodium hydrogen sulphite separated from water as needles, m. p. 175° (decomp.), and retained a small amount of water of crystallisation after drying *in vacuo* (Found : C, 30·5; H, 2·25. $C_8H_7O_5Cl_2SNa,\frac{1}{4}H_2O$ requires C, 30·65; H, 2·4%); the 2 : 4-*dinitrophenylhydrazone* separated from benzene–light petroleum as needles, m. p. 169° (Found : N, 14·6. $C_{14}H_{10}O_8N_4Cl_2$ requires N, 14·55%); 2 : 4 : 5-*trichlorophenoxyacetaldehyde* (17·6 g. from 27·15 g. of ether), b. p. 132—135°/1 mm., separated from light petroleum as needles, m. p. 109—110° (Found : C, 40·15; H, 2·2. $C_8H_5O_2Cl_3$ requires C, 40·1; H, 2·1%); the *adduct hydrate* with sodium hydrogen sulphite separated from water as plates, m. p. 183—184° (Found : C, 26·65; H, 2·2. $C_8H_6O_5Cl_3SNa,H_2O$ requires C, 26·55; H, 2·25%), and the 2 : 4-*dinitrophenylhydrazone* as needles, m. p. 167—168°, from benzene–light petroleum (Found : C, 40·15; H, 2·3; N, 13·1. $C_{14}H_9O_5N_4Cl_3$ requires C, 40·05; H, 2·15; N, 13·35%).

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Quassin and neo*Quassin. Part II.**

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[Reprint Order No. 5469.]

A phenol formed by the dehydrogenation of *neo*quassin with selenium (Part I, *loc. cit.*) has been shown to be 3 : 4 : 5-trimethylguaiacol (V).

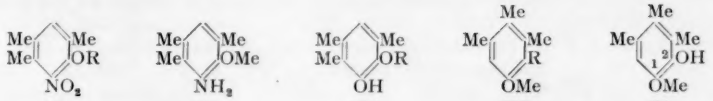
ON being heated with selenium *neo*quassin, a reduction product of quassin, gave rise to the monomethyl ether of a dihydric phenol. This had the formula $C_9H_{11}O{\cdot}OMe$, m. p. 70°, and gave a greenish-yellow ferric reaction (Part I, *J.*, 1950, 3431). Apparently an integral part of the quassin and *neo*quassin molecule, this product was considered to be a derivative of guaiacol or of resorcinol monomethyl ether, but did not appear to be identical with any of the known isomeric C_3 derivatives of these phenols.

In the present work, since the ferric reaction was more in keeping with that of a guaiacol than of a resorcinol derivative, attention was primarily directed to the preparation of the unknown C_3 alkylguaiacols. Of the eight propylguaiacols the hitherto unknown 4- and 6-*iso*propylguaiacol have been synthesised by standard methods, but neither was identical with the dehydrogenation product.

Whilst these experiments were in progress the small amount of the phenol, m. p. 70°, available was re-examined and found to give a blue-violet colour with 2 : 6-dichloroquinone chloroimide (Gibbs's reagent), indicating the absence of a substituent in the *p*-position to the hydroxyl group, and to couple with the *p*-nitrobenzenediazonium chloride. Subsequently, the dehydrogenation of *neo*quassin was carried out on a larger scale and from the phenolic fraction, which was isolated and purified by a somewhat modified procedure (cf. Part I, *loc. cit.*), there was obtained a phenol, $C_9H_{11}O{\cdot}OMe$, m. p. 74·5°, with a pale green ferric

* Part I, *J.*, 1950, 3431.

reaction, which on admixture did not depress the melting point of the earlier specimen. This product, however, gave a negative fluorescein and Gibbs's reaction, and did not react with toluene-*p*-diazonium chloride under the usual conditions; the positive reactions given by the earlier specimen appear to have been due to traces of impurities, probably arising by the distillation of the crude dehydrogenation product over sodium. On demethylation the phenol, m. p. 74·5°, gave a dihydric phenol, m. p. 93°, which had a deep green ferric reaction and on being kept decomposed in aqueous solution. From these results it appeared likely that the phenol was either a trimethyl-, type (III) or (V), or an ethylmethyl-guaiacol.



The precursor (I; R = Me) required for the preparation of (III; R = Me) and (III; R = H) has been obtained from *ψ*-cuminol by Auwers (*Ber.*, 1884, **17**, 2979; 1885, **18**, 2658; 1896, **29**, 1105) but, as difficulties were encountered in the nitration of *ψ*-cuminol to the required intermediate quinitrol, the compound (III; R = Me) was prepared from 6-nitro-*ψ*-cumidine by way of the stages (I; R = H), (I; R = Me), and (II). The guaiacol (III; R = Me) and the parent catechol (III; R = H) were similar to, but not identical with, the phenol, m. p. 74·5°, and its demethylation product respectively. By a similar procedure (IV; R = NO_2), obtained from 3 : 4 : 5-trimethyl-2-nitrophenol, was converted by way of (IV; R = NH_2) into 3 : 4 : 5-trimethylguaiacol (V) which was identical with the dehydrogenation product, m. p. 74·5°, giving the same carbanilate and the same ultra-violet absorption spectra.

The two isomeric monomethyl ethers of 4-*n*-propylresorcinol were synthesised by standard methods in the course of comparing the phenol from *neo*quassin with some of the isomeric alkylresorcinols.

Experimental

2-*Amino*-3 : 4 : 6-*trimethylanisole* (II).—6-Nitro-*ψ*-cumidine (Heunder, *Rec. Trav. chim.*, 1915, **34**, 11) (5 g.), dissolved in 20% sulphuric acid (50 ml.), was diazotised at 0—5° with a solution of sodium nitrite (2 g.) in water (25 ml.) and the mixture added to a boiling saturated solution of copper sulphate in water (100 ml.) during 5 min. Next day the product was isolated with ether and purified by means of dilute aqueous sodium hydroxide and then by crystallisation from dilute alcohol, giving 6-nitro-*ψ*-cuminol in orange prisms (1·9 g.), m. p. 46—47°, which with diazomethane gave the monomethyl ether, m. p. 39—40° (cf. Auwers, *loc. cit.*). Decomposition of the diazonium salt with steam, with boiling sulphuric acid containing sodium sulphate, or by the methods of Orton *et al.* (*J.*, 1907, **91**, 35) gave poor yields (*ca.* 10%) of the required phenol, probably owing in part to a tendency to indazole formation.

Reduction of this ether (4·2 g.), in methanol (70 ml.), with hydrogen and palladium–charcoal furnished 6-*amino*-2 : 4 : 5-*trimethylanisole* as a colourless oil (1·9 g.), b. p. 132°/12 mm. (Found : N, 8·5; OMe, 18·5. $C_9H_{12}N{\cdot}OMe$ requires N, 8·4; OMe, 18·2%).

3 : 4 : 6-*Trimethylcatechol* (III; R = H).—Prepared at 0—5° from 6-amino-2 : 4 : 5 trimethylanisole (1·6 g.), dissolved in a mixture of concentrated sulphuric acid (2 ml.) and water (14 ml.), with a solution of sodium nitrite (0·7 g.) in water (10 ml.), the solution of the diazonium salt was added dropwise to a boiling saturated solution of copper sulphate (*ca.* 50 ml.) in a distilling flask. From the distillate 3 : 4 : 6-*trimethylguaiacol* was isolated with ether and purified by means of aqueous sodium hydroxide and then by crystallisation from dilute methanol, forming rods (0·85 g.), m. p. 84° (Found, in specimen sublimed at 60°/0·1 mm.: C, 72·4; H, 8·5. $C_{10}H_{14}O_2$ requires C, 72·3; H, 8·4%). This phenol gives a green ferric reaction in alcohol and a blue colour with Gibbs's reagent. On demethylation with boiling concentrated hydriodic acid and acetic acid for 30 min. the compound furnished 3 : 4 : 6-trimethylcatechol which on repeated sublimation at 80°/0·001 mm. formed colourless needles, m. p. 118—120°, with a green ferric reaction in alcohol.

2-*Amino*-3 : 4 : 5-*trimethylanisole* (IV; R = NH_2).—Methylated with ethereal diazomethane, 3 : 4 : 5-trimethyl-2-nitrophenol (Auwers, *Fortschr. Chem.*, 1926, **18**, 26) (2·4 g.) gave 3 : 4 : 5-*trimethyl*-2-*nitroanisole* which separated from methanol in pale yellow rods (2·1 g.), m. p. 162—164° (Found : N, 7·5; OMe, 16·1. $C_9H_{10}O_2N{\cdot}OMe$ requires N, 7·2; OMe, 15·9%). Reduction of this compound (2 g.) with hydrogen and palladium–charcoal furnished 2-*amino*-3 : 4 : 5-*trimethylanisole* as a colourless oil (0·82 g.), b. p. 155—160/15 mm. (Found : N, 8·6; OMe, 18·8. $C_9H_{13}N{\cdot}OMe$ requires N, 8·4; OMe, 18·2%). Purified by sublimation in a high vacuum, the *acetyl* derivative had m. p. 154° (Found : OMe, 14·7. $C_{16}H_{16}ON{\cdot}OMe$ requires OMe, 15·0%).

3 : 4 : 5-*Trimethylguaiacol* (V).—(*a*) 2-Amino-3 : 4 : 5-trimethylanisole (0·8 g.) was diazotised and converted into 3 : 4 : 5-trimethylguaiacol by the procedure employed for the preparation of 3 : 4 : 6-trimethylguaiacol. Purified by sublimation in a vacuum and then by crystallisation from dilute methanol, 3 : 4 : 5-*trimethylguaiacol* formed slender needles (436 mg.), m. p. 74°, $\lambda_{max.}$ 284 (log ε 3·37), $\lambda_{min.}$ 253 (log ε 2·52) (Found : C, 72·3; H, 8·4; OMe, 18·7. $C_9H_{11}O{\cdot}OMe$ requires C, 72·3; H, 8·4; OMe, 18·7%). The *carbanilate* of this phenol separated from light petroleum (b. p. 60—80°) in prisms, m. p. 142—143° (Found : N, 5·1. $C_{17}H_{19}O_3N$ requires N, 4·9%).

(*b*) The product obtained by heating a mixture of *neo*quassin (20 g.) and selenium (30 g.) at 295—305° for 20 hr. (Part I, *loc. cit.*) was distilled and a solution of the fraction, b. p. 100—200°/15 mm., in light petroleum (b. p. 40—60°) was extracted with several small portions of 2N-sodium hydroxide, and the combined extracts were acidified. From this an oil was isolated with ether which on distillation gave a semi-solid fraction (0·2 g.), b. p. 100—150°/15 mm. Recrystallised from light petroleum (b. p. 40—60°) and then dilute methanol this product furnished 3 : 4 : 5-trimethylguaiacol in needles, m. p. 74·5—75° undepressed on admixture with synthetical material, $\lambda_{max.}$ 285 (log ε 3·38), $\lambda_{min.}$ 253 (log ε 2·49) (Found : C, 72·6; H, 8·4%). Like the synthetic compound, the phenol gave a pale green ferric reaction and a negative Gibb's and fluorescein reaction. The carbanilate had m. p. and mixed m. p. 142—143°.

Demethylation of 3 : 4 : 5-trimethylguaiacol (35 mg.) by the method employed for 3 : 4 : 6-trimethylguaiacol gave 3 : 4 : 5-trimethylcatechol which was purified by distillation in a high vacuum and then crystallisation from light petroleum (b. p. 40—60°), having m. p. 86—89° and a green ferric reaction.

2-*Nitro*-4-iso*propylanisole*.—Nitric acid (37 g., diluted with 37 g. of water) was added to a well-stirred solution of *p-iso*propylphenol (25 g.) in benzene (50 g.) at 20° in 1 hr., and an hour later the benzene solution was separated, washed, and distilled with steam. A dried ethereal extract of the distillate was evaporated, leaving an oil which on distillation gave 2-*nitro*-4-iso*propylphenol* as a pale yellow oil (19·8 g.), b. p. 131—133°/19 mm. (Found : N, 7·9. $C_9H_{11}O_3N$ requires N, 7·7%). Purified by chromatography from benzene on aluminium oxide and then from light petroleum (b. p. 40—60°), the *benzoate* formed colourless needles, m. p. 61° (Found : N, 5·0. $C_{16}H_{15}O_4N$ requires N, 4·9%).

Methylation of 2-nitro-4-*iso*propylphenol (19·5 g.) was effected with methyl sulphate (28 g.) and potassium carbonate (38·5 g.) in boiling xylene (30 ml.) for 22 hr. After the removal of the solvent with steam the product was isolated with ether, washed with 2N-sodium hydroxide, and distilled, giving 2-*nitro*-4-iso*propylanisole* as a pale yellow oil (15·1 g.), b. p. 166—168°/11 mm. (Found : N, 7·5. $C_{10}H_{13}O_3N$ requires N, 7·2%).

4-iso*Propylguaiacol*.—2-Nitro-4-*iso*propylanisole (15 g.) was reduced in methanol (100 ml.) with hydrogen and palladium–charcoal (from 1 g. of charcoal and 0·5 g. of palladium chloride), and the product purified by way of the hydrochloride and then by distillation, giving 2-amino-4-*iso*propylanisole as a colourless wax-like solid (8·4 g.), b. p. 138°/15 mm., m. p. 36—37°. Purified by chromatography from benzene on aluminium oxide and then from aqueous methanol, the benzoyl derivative formed needles, m. p. 67—68° (Found : N, 5·2; OMe, 12·6. $C_{16}H_{16}ON{\cdot}OMe$ requires N, 5·2; OMe, 11·5%).

A solution of 2-amino-4-*iso*propylanisole (8·2 g.) in 50% sulphuric acid (16 g.) and water (80 ml.) at 0° was treated with sodium nitrite (4 g.) in water (40 ml.), and the mixture added drop-wise to boiling 60% sulphuric acid (400 ml.). Isolated with steam, followed by extraction with ether, the resulting 4-iso*propylguaiacol* was purified by way of the sodium salt, then by distillation and by crystallisation from dilute methanol, forming large micaceous plates (4·7 g.), m. p. 39°, with a pale green ferric reaction in alcohol (Found : C, 71·9; H, 8·3; OMe, 18·3. $C_9H_{11}O{\cdot}OMe$ requires C, 72·3; H, 8·4; OMe, 18·7%). Purified by chromatography from benzene and then by crystallisation from dilute methanol, the *benzoate* formed shining rectangular plates, m. p. 66° (Found : C, 75·1; H, 6·5; OMe, 11·6. $C_{16}H_{15}O_2{\cdot}OMe$ requires C, 75·5; H, 6·7; OMe, 11·5%).

6-iso*Propylguaiacol*.—Prepared from 2-*iso*propylphenol (Niederl and Storch, *J. Amer. Chem. Soc.*, 1933, **55**, 292), 6-nitro-2-*iso*propylphenol (Fileti, *Gazzetta*, 1886, **16**, 121) (5·2 g.) was esterified with diazomethane, giving 6-*nitro*-2-iso*propylanisole* as an oil, b. p. 140°/15 mm. (Found : N, 7·4; OMe, 15·4. $C_9H_{10}O_2N$·OMe requires N, 7·2; OMe, 15·9%). Catalytic reduction of this compound (4·1 g.) furnished 6-amino-2-*iso*propylanisole as a pale yellow oil (2·4 g.), b. p. 117—120°/15 mm., which gave a *benzoyl* derivative forming irregular plates, m. p. 100—101°, from aqueous methanol after having been chromatographed from benzene on aluminium oxide (Found : N, 5·2; OMe, 11·5. $C_{16}H_{16}ON$·OMe requires N, 5·2; OMe, 11·5%).

6-Amino-2-*iso*propylanisole (2·3 g.) was diazotised and converted into 6-iso*propylguaiacol* by the procedure employed for 2-amino-4-*iso*propylanisole. The phenol separated from light petroleum (b. p. 40—60°) in needles (0·7 g.), m. p. 63—64°, having a very faint green ferric reaction (Found : C, 72·2; H, 8·3; OMe, 18·8%).

5-*Methoxy*-2-n-*propylphenol*.—A mixture of 2 : 4-dihydroxy-*n*-propiophenone (Brewster and Harries, *J. Amer. Chem. Soc.*, 1930, **52**, 4866) (7 g.), methyl iodide (6 ml.), potassium carbonate (13 g.), and acetone (50 ml.) was heated under reflux for 2½ hr. On isolation the resulting 2-hydroxy-4-methoxy-*n*-propiophenone formed plates (4·2 g.), m. p. 58°, from alcohol (cf. Tahara, *Ber.*, 1892, **25**, 1298). Reduction of this ketone (2 g.) with amalgamated zinc (10 g.) and 15% hydrochloric acid (20 ml.) at room temperature for 16 hr. and then under reflux for 2 hr. gave 5-*methoxy*-2-n-*propylphenol*, forming plates (1·7 g.), m. p. 45°, from light petroleum (b. p. 40—60°), with a negative ferric reaction (Found : C, 72·4; H, 8·6. $C_{10}H_{14}O_2$ requires C, 72·3; H, 8·4%).

3-*Methoxy*-4-n-*propylphenol*.—Partial benzylation of 2 : 4-dihydroxy-*n*-propiophenone (6 g.), with benzyl chloride (6·8 g.) and potassium carbonate (12 g.) in boilihg acetone for 2 hr., gave 4-*benzyloxy*-2-*hydroxy*-n-*propiophenone*, forming plates (7·0 g.), m. p. 112—114°, from methanol, with a red-purple ferric reaction (Found : C, 74·7; H, 6·3. $C_{16}H_{16}O_3$ requires C, 75·0; H, 6·3%). The 2 : 4-*dinitrophenylhydrazone* separated from ethyl acetate in bright red needles, m. p. 203° (Found : N, 13·0. $C_{22}H_{20}O_6N_4$ requires N, 12·8%).

Methylation of the benzyl ether (5 g.) by the methyl iodide–potassium carbonate method for 36 hr. gave 4-*benzyloxy*-2-*methoxy*-n-*propiophenone*, forming long needles (4·8 g.), m. p. 59—60°, from light petroleum (b. p. 60—80°) (Found : C, 75·3; H, 6·5. $C_{17}H_{18}O_3$ requires C, 75·6; H, 6·7%). The 2 : 4-*dinitrophenylhydrazone* separated from methanol in orange needles, m. p. 129—131° (Found : N, 12·4. $C_{23}H_{22}O_6N_4$ requires N, 12·4%).

Debenzylation of this ether (4 g.) with acetic acid (40 ml.) and concentrated hydrochloric acid (27 ml.) at 100° for ½ hr. gave 4-*hydroxy*-2-*methoxy*-n-*propiophenone* which was distilled at 140°/0·001 mm. and then crystallised from ethyl acetate–light petroleum (b. p. 60—80°), forming prisms, m. p. 114—116° (Found : C, 66·4; H, 6·7; OMe, 17·1. $C_9H_9O_2$·OMe requires C, 66·6; H, 6·7; OMe, 17·2%). Reduction of this ketone (1 g.) by the Clemmensen method gave 3-*methoxy*-4-n-*propylphenol*, which on distillation at 110°/0·002 mm. followed by crystallisation from light petroleum (b. p. 40—60°) formed micaceous plates (0·6 g.), m. p. 51—53°, with a negative ferric reaction (Found : C, 72·1; H, 8·3; OMe, 18·7. $C_9H_{11}O$·OMe requires C, 72·3; H, 8·4; OMe, 18·7%).

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The Mechanism of Decomposition of Potassium Permanganate in Alkaline Solution. Part II. The Use of Water Enriched in ^{18}O as Solvent.*

By M. C. R. Symons.

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Oxygen obtained as a product of the reaction $4MnO_4^- + 4OH^- \longrightarrow 4MnO_4^{2-} + 2H_2O + O_2$, in which the solvent was enriched in ^{18}O, has been found, by mass-spectrometric analysis, to have the same percentage isotopic enrichment as the solvent. The manganate was partially enriched in ^{18}O if isolated by precipitation as barium manganate after the reaction was complete, but had negligible enrichment if the reaction mixture contained barium ions, so that the manganate was precipitated as soon as it was formed. It is therefore concluded that the oxygen came entirely from the solvent, as required by the reaction sequence proposed in Part I.* The significance of the observed oxygen exchange between manganate and the solvent is discussed. Further observations on the initiation of polymerisation of acrylonitrile and styrene are reported.

In Part I*, a spectrophotometric study of the reaction $4MnO_4^- + 4OH^- \longrightarrow 4MnO_4^{2-} + 2H_2O + O_2$ was described, and it was concluded that the kinetic results obtained for the first 65% of the decomposition were best interpreted by the reaction sequence:

$$(1) \quad MnO_4^- + OH^- \rightleftharpoons MnO_4^{2-} + \cdot OH$$

$$(2) \quad \cdot OH + OH^- \rightleftharpoons \cdot O^- + H_2O$$

$$(3) \quad MnO_4^- + OH^- + \cdot O^- \rightleftharpoons MnO_4^{2-} + HO_2^-$$

$$(4) \quad MnO_4^- + HO_2^- \rightleftharpoons MnO_4^{2-} + HO_2\cdot$$

$$(5) \quad HO_2\cdot + OH^- \rightleftharpoons O_2^- + H_2O$$

$$(6) \quad MnO_4^- + O_2^- \longrightarrow MnO_4^{2-} + O_2$$

No information regarding the stereochemistry of the postulated exchange reactions can be obtained from kinetic results, but it was thought that a knowledge of the isotopic enrichment of oxygen evolved from a reaction occurring in water enriched in ^{18}O might shed some light on this aspect of the reaction.

Cahill and Taube (*J. Amer. Chem. Soc.*, 1952, **74**, 2312) found that when permanganate reacts with hydrogen peroxide the oxygen evolved is derived entirely from the latter. The reaction sequence (4)—(6) is in accord with this observation. However, Mills (*ibid.*, 1940, **62**, 2833) found that considerable oxygen exchange occurred when potassium permanganate was heated in water for 1 hr. at 100°, whilst Hall and Alexander (*ibid.*, p. 3455) observed partial exchange when sodium permanganate was kept for 4 hr. at 95°, and that this exchange was increased in the presence of 0·2N-sodium hydroxide. No observations on oxygen exchange between manganate and water have been recorded. It was thus necessary that the amount of oxygen exchange occurring between permanganate or manganate and the solvent during the reaction should also be determined.

Water having an oxygen enrichment of 0·84 atom % of ^{18}O was used, and the oxygen evolved was analysed mass spectrometrically. The manganate formed was precipitated as barium manganate by addition of saturated barium hydroxide solution, and this was heated *in vacuo* until oxygen was evolved. The resulting oxygen was analysed as before.

Oxygen evolved during the decomposition of permanganate was found to have an enrichment identical with that of the solvent, whilst oxygen derived from the decomposition of barium manganate had an enrichment which varied with experimental conditions, the largest observed being about 50% of the enrichment of the solvent. Since

* The communication "The Mechanism of Decomposition of Potassium Permanganate in Alkaline Solution," *J.*, 1953, 3956, is regarded as Part I.

it was considered probable that this latter enrichment had occurred by exchange between manganate ions and the solvent, rather than either between permanganate ions and the solvent or as a direct result of the reaction, a quantity of barium hydroxide equivalent to the permanganate was added to the solution of sodium hydroxide before mixing, so that the manganate ion was precipitated as formed. Under these conditions, the enrichment in the manganate produced was negligible. Typical results are as follows :

	O_2 from $KMnO_4$	O_2 from $BaMnO_4$ (i)	O_2 from $BaMnO_4$ (ii)
Mass ratio, 32/34	49	81	228
Atom %, enrichment	0·85	0·44	0·03

(i) Formed after reaction. (ii) Formed during reaction.

It is, therefore, concluded that permanganate ion does not exchange oxygen with the solvent under the conditions used but that considerable oxygen exchange between manganate and the solvent does occur unless the manganate is present only as insoluble barium manganate. Thus, since the oxygen evolved has the same enrichment as the solvent, it is concluded that this oxygen is derived entirely from the solvent, and not at all from the permanganate.

Discussion.—Mills (*loc. cit.*) and Edwards (*Chem. Reviews*, 1952, **50**, 466) have discussed possible mechanisms for oxygen exchange between oxy-anions and water, and conclude that the most probable mechanism involves protonation, followed by anhydride formation. The exchange by permanganate ion in neutral and alkaline solution observed by Mills and by Hall and Alexander is, therefore, anomalous, since permanganic acid is a very strong acid. However, electron exchange between permanganate and manganate ions is very rapid (Adamson, *J. Phys. Colloid Chem.*, 1951, **55**, 293; Sheppard and Wahl, *J. Amer. Chem. Soc.*, 1953, **75**, 5133) and manganate has now been found to exchange oxygen with the solvent even in strongly alkaline solution, so that if only small quantities of manganate were formed in the solution used, apparent exchange by the permanganate ion would be expected. This mechanism for exchange would be in accord with the alkaline catalysis observed by Hall and Alexander.

Chromate ion, which closely resembles manganate ion in structure, has been found by Winter, Carlton, and Briscoe (*J.*, 1940, 131) to undergo complete oxygen exchange after 24 hr. at 100° in N-alkali. These authors consider that exchange occurs *via* the equilibrium $Cr_2O_7^{2-} + H_2O \rightleftharpoons 2HCrO_4^-$, but Mills (*loc. cit.*) favours the equilibrium $HCrO_4^- + H^+ \rightleftharpoons CrO_3 + H_2O$.

An alternative mechanism for exchange by these ions is that one water molecule or hydroxide ion displaces another by a process of S_N2 type :

$$*OH^- + HOMnO_3^- \rightleftharpoons H*OMnO_3^- + OH^-$$

The transition state for a displacement of this type could be stabilised by the use of vacant inner or outer *d*-orbitals of the central atom, and this stabilisation should be greatest for elements near the bottom of the Periodic Table. In fact, such stabilisation is so great for periodate and per-rhenate ions that hydrated ions such as $H_4IO_6^-$ and ReO_5^{3-} are stable species.

Certain observations by Hall and Alexander (*loc. cit.*) lend further support to this theory : for instance, although chlorate and perchlorate ions undergo negligible exchange in neutral or alkaline solution, yet bromate and iodate ions undergo considerable exchange and this is catalysed by alkali.

The mechanism for stage (1) in the decomposition of permanganate is now discussed in the light of these considerations. Thus, even if π-bonding between manganese and the four oxygen atoms in the permanganate ion is complete, as postulated by Wolfsberg and Helmholz (*J. Chem. Phys.*, 1952, **20**, 837), there still remains one vacant inner *d*-orbital which could, conceivably, be used for bonding to a hydroxide ion in the transition state. However, if such a complex were formed, it must be such that proton exchange cannot

occur before decomposition, since this would result in oxygen exchange by the manganate or permanganate ions :

$$HO^{*-} + MnO_4^- \rightleftharpoons H^*OMnO_4^{2-} \rightleftharpoons H^*O\cdot + MnO_4^{2-}$$

$$\Updownarrow$$

$$HO^- + Mn^*O_4^- \rightleftharpoons HOMnO^*_4{}^{2-} \rightleftharpoons HO\cdot + MnO^*_4{}^{2-}$$

(compare Bender, *J. Amer. Chem. Soc.*, 1951, **73**, 1626).

Reaction with Vinyl Monomers.—In an attempt to gain further evidence of the presence of free-radical intermediates which may be formed during the decomposition of permanganate in alkaline solution, interaction between this system and vinyl monomers, first mentioned in a preliminary report (Symons, *Research*, 1953, **6**, 5s), has been further studied. In view of the evident complexity of the reactions, any attempt at interpretation of experiments must be extremely tentative.

Experimental

The methods used for purifying the water and the potassium permanganate and for cleaning all glass apparatus are described in Part I (*loc. cit.*). Sodium was distilled under 0·002 mm. in dry, oxygen-free nitrogen, and stored in glass tubes, the procedure described by Dostrovsky and Llewellyn (*J. Soc. Chem. Ind.*, 1949, **68**, 208) being used. The weight of sodium used was estimated approximately by measuring the length of tubing. This tube was broken into short lengths in an atmosphere of nitrogen and added directly to the enriched water, through which a rapid stream of nitrogen was passing.

The resulting sodium hydroxide solution (10 c.c.; about 5N) was placed in a round-bottomed flask (20 c.c.) fitted with a side arm containing finely powdered potassium permanganate (0·3 g.). This flask was then connected *via* a three-way tap to a breaker-seal tube (10 c.c.). After the solution had been de-aerated by repeated cooling in acetone–carbon dioxide, followed by evacuation to 0·002 mm., the reactants were mixed and the flask was gently shaken until the potassium permanganate had dissolved. The flask was then heated at 60° until reaction was complete (2—4 hr.). The solution was then cooled in freezing mixture to remove water vapour, and the evolved oxygen was allowed to pass into the evacuated breaker-seal tube. In some experiments " AnalaR " grade solid barium hydroxide was dissolved in the solution of sodium hydroxide before mixing; in others, the residual alkaline solution containing manganate was added to an excess of saturated barium hydroxide solution. In either case, the precipitated barium manganate was removed by filtration through sintered glass, dried at 120°, and sealed into an evacuated Pyrex tube (10 c.c.) connected to a breaker-seal tube. After being heated to a red heat until evolution of oxygen was complete, the reaction tube was immersed in freezing mixture to remove any water vapour, and the breaker-seal tube detached.

Reactions with Acrylonitrile and Styrene.—The monomers were purified by washing with dilute alkali and water, followed by distillation under a reduced pressure of nitrogen. Since the solubility of acrylonitrile and styrene in strongly alkaline solution (about 3N) is small, the mixtures were vigorously stirred and, in some instances, a trace of sodium dodecyl sulphate was added as an emulsifying agent. Dilute potassium permanganate solution was added dropwise at room temperature, the total amount added being about one-tenth of the molar concentration of monomer. Throughout the reaction (about ½ hr.) a vigorous stream of nitrogen was bubbled through the solution.

The results obtained with acrylonitrile were as previously reported (Symons, *loc. cit.*), no polymer being formed without prior neutralisation. With styrene, however, reduction of permanganate was comparatively slow at room temperature and did not proceed beyond the manganate stage. After reaction, it was observed that small globules of coagulated polymer sank to the bottom of the flask. The upper layer of styrene was separated and dissolved in acetone. Addition of aqueous acetone gave a further precipitation of polymer. However, acidification of the remaining alkaline solution gave carbon dioxide and benzoic acid, showing that extensive oxidation of the styrene had also occurred. Again, permanganate added to a neutral emulsion of styrene in water was rapidly reduced to manganese dioxide but polymerisation was not observed.

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THE UNIVERSITY, SOUTHAMPTON. [*Received, March 31st,* 1954.]

The Kinetics and Mechanisms of Nucleophilic Displacements in Allylic Systems. Part VII. Solvent Effects in the Reactions of the Dichloropropenes and Related Compounds.*

By P. B. D. DE LA MARE and C. A. VERNON.

[Reprint Order No. 5371.]

Since *trans*-1 : 3-dichloropropene releases 50% of its chlorine on solvolysis in aqueous ethanol, it may be deduced that this reaction is a first-order bimolecular solvolysis. The extent by which the rate of the reaction is increased by alkali may be used as a guide in the examination of other compounds, in which the molecularity of the solvolysis is difficult to determine. Misconceptions concerning the mechanisms and products of the reactions of 3 : 3- and 1 : 3-dichloropropene are corrected. Solvent effects on the S_N2 reactions of these compounds with nucleophilic reagents, and on the S_N2' reactions of 3 : 3-dichloroprop-1-ene and of 3 : 3 : 3-trichloro-2-methylprop-1-ene with thiophenoxide ions, are discussed.

To decide whether the first-order solvolysis of an organic chloride is uni- or bi-molecular is frequently difficult. This problem becomes particularly acute in dealing with allyl and substituted allyl halides, since the allyl structure favours both S_N1 and S_N2 mechanisms. Kirrmann, Schmitz, and Saito (*Bull. Soc. chim.*, 1952, **19**, 515) recently discussed the solvolyses of allyl halides in ethanol, ethanol–water mixtures, and dioxan–water mixtures, and concluded that the first-order reactions observed in the absence of alkali are probably unimolecular.

In earlier papers (Parts I, II, and IV, de la Mare and Vernon, *J.*, 1952, 3325, 3331; 1953, 3555), the bimolecular reactions of 3 : 3-dichloroprop-1-ene in ethanol were discussed, and it was shown that the S_N2' reaction is of considerable importance; on the other hand, allylic rearrangement was by no means complete, but represented in general less than 50% of the total reaction. Theoretical considerations would suggest that allylic shift should also be incomplete in most systems under conditions of unimolecular solvolysis; for, as is well exemplified by examples from the literature (cf. Ingold, " Structure and Mechanism in Organic Chemistry," G. Bell and Sons Ltd., London, 1953, pp. 586—590), the unimolecular solvolysis of an allylic halide gives a mesomeric cation, which may react at either of the potential carbonium ionic centres to give a mixture of isomeric products. Kirrmann, Schmitz, and Saito (*loc. cit.*) claim, however, that this compound is solvolysed unimolecularly with total allylic shift, which, they consider, is scarcely compatible with a bimolecular reaction of this compound. This claim deserves further attention, therefore, more especially since earlier work (cf. Kirrmann, Pacaud, and Dosque, *Bull. Soc. chim.*, 1934, **1**, 860) suggests that the products of allylic rearrangement are in a wide range of examples formed in poor yield.

The 1 : 3-dichloropropenes are also of particular interest; for with these compounds, the S_N2 reaction releases initially only one chlorine atom, whereas the S_N1 reaction will in general lead to the release of more than one equivalent of chlorine, with the corresponding formation of derivatives of acraldehyde. With these compounds, in contrast with the behaviour of 3 : 3-dichloroprop-1-ene, the S_N2 reaction is sufficiently rapid to obscure completely any S_N2' reaction. Hence release of one equivalent of chloride from the

* Part VI, *J.*, 1954, 2504.

compound may be taken as diagnostic of the S_N2 reaction, even in solvolyses, in which the ordinary kinetic tests are unavailable.

Investigation and clarification of these points, as discussed in more detail below, have led us also to document more fully the effect of changes of solvent on the rates of S_N2 and S_N2' reactions of allylic halides.

Experimental

(a) *Material and Methods.*—Most of these have been described in previous papers (de la Mare and Vernon, *locc. cit.*; Part III, *J.*, 1952, 3628; Part VI, *loc. cit.*; Part V, Vernon, *J.*, 1954, 423). Solutions of sodium formate in formic acid were prepared by dissolving sodium metal in the anhydrous acid. 1-Chloro-3-hydroxyprop-1-ene, prepared from 1 : 3-dichloropropene and sodium carbonate, had b.p. 85°/57 mm., n_D^{25} 1·4657.

(b) *Reactions of* 3 : 3-*Dichloroprop*-1-*ene in Ethanol–Water Mixtures.*—The following are details of the rate of production of acid by the solvolysis of 3 : 3-dichloroprop-1-ene in 50% ethanol * at 64·0°. Samples (5·17 ml.) were removed at intervals for titration with 0·0165N-sodium hydroxide :

Time (min.)	0·0	20·0	93·0	142	199	281	1445	1589	∞
Titre (ml.)	0·70	1·32	2·81	4·02	4·92	6·69	17·93	18·64	22·04
10^3k_1 (min.$^{-1}$)	—	1·02	1·12	1·19	1·11	1·17	1·14	1·15	—

Values of k_1 are calculated from the formula $k_1 = 2{\cdot}303\ \{\log_{10} H_\infty{}^+/(H_\infty{}^+ - H_t{}^+)\}/t$. Separate experiments showed that the stable infinity-value for the development of acid (in agreement with the value obtained by titration of liberated chloride) represented the release of 59·3% of the chlorine in the organic chloride, and hence represented the formation of 82% of rearranged products. The mean rate coefficient ($k_1 = 0{\cdot}00113$ min.$^{-1}$) was unaffected by the addition initially of 0·080N-hydrochloric acid, and was increased only slightly (to $k_1 = 0{\cdot}00141$ min.$^{-1}$) by the presence initially of 0·15N-potassium hydroxide; under the latter conditions, the release of chloride was increased slightly, to about 63%, presumably by incursion of a bimolecular reaction. Values at other temperatures ($k_1 = 0{\cdot}0092$ min.$^{-1}$ at 84·6°; 0·000133 min.$^{-1}$ at 44·6°) lead to a value of $E = 23{\cdot}5$ kcal./mole.

Despite the report, made by Kirrmann, Schmitz, and Saito (*loc. cit.*; cf. Pourrat and Schmitz, *Bull. Soc. chim.*, 1952, **19**, 525; Schmitz, *ibid.*, p. 509), to the contrary, the product of normal substitution can be obtained from this reaction. 3 : 3-Dichloroprop-1-ene (2 ml.) was refluxed for 4 hr. with 200 ml. of 50% ethanol in the presence of 10 g. of barium carbonate, added to keep the solution neutral. The alcohol and the acraldehyde were then distilled off into excess of a 0·1% solution of 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid. Filtration gave the 2 : 4-dinitrophenylhydrazone of acraldehyde (0·45 g., yield *ca.* 50%, assuming 18% of unrearranged product); this, after recrystallisation from aqueous ethanol, had m. p. 157°, unchanged on admixture with an authentic specimen. Treated in the same way, neither *cis*- nor *trans*-1 : 3-dichloropropene gave more than a trace (<0·05 g.) of 2 : 4-dinitrophenylhydrazone.

The reaction of 3 : 3-dichloroprop-1-ene in 75% ethanol with sodium thiophenoxide (0·309N) at 45·7° was followed as described in Part II (*loc. cit.*). The infinity-value, stable over the range 10—30 half-lives for the reaction, represented the liberation of 86·4% of the chlorine in the compound. This value being assumed, the total second-order rate coefficient, substantially constant over 80% reaction, was found to be $k_2 = 0{\cdot}190$ l. mole^{-1} min.$^{-1}$.

(c) *Reactions of* trans-1 : 3-*Dichloropropene in Ethanol–Water Mixtures.*—Determination of the percentage release of chloride from this compound gave the following results. In 50% ethanol, at 64·9°, 49·4%; + 0·025N-KOH, 48·9%. In 75% ethanol, at 64°, 49·7%; + 0·025N-KOH, 49·8%. Rate coefficients for these reactions are included in later Tables in the discussion. The following data show the very small extent to which the solvolysis results in the production of derivatives of acraldehyde. 1 : 3-Dichloropropene was allowed to solvolyse in 50% ethanol at 100°, and at intervals, samples were removed for the determination (*a*) of chloride and (*b*) of acraldehyde and its derivatives, by comparison with standard acraldehyde solutions, the method adapted from that of Circle, Stace, and Boruff (*Ind. Eng. Chem. Anal.*, 1945, **17**, 259), described in Part I (*loc. cit.*), being used.

* A solvent "x% ethanol" is a mixture of x parts by vol. of ethanol with (100−x) parts by vol. of water.

The fact that the ratio of acraldehyde derivatives to chloride rises towards the end of the reaction suggests that the small amount produced, or at least a substantial part of it, comes

Time (min.)	0·00	6·0	9·0	12·0	15·0	18·0
Cl^- (ml. 0·01N-$AgNO_3$)	0·72	1·72	2·12	2·45	3·03	3·45
$10k_1$ ($min.^{-1}$)	—	1·52	1·45	1·37	1·50	1·51
[Deriv. of acraldehyde]/[Cl^-]	—	0·00	0·00	0·00	0·00	0·006
Time (min.)	23·0	28·0	35·0	78·0	106·0	∞
Cl^- (ml. 0·01N-$AgNO_3$)	4·02	4·62	5·38	8·55	9·65	12·18
$10k_1$ ($min.^{-1}$)	1·48	1·48	1·49	1·47	1·47	—
[Deriv. of acraldehyde]/[Cl^-]	0·007	0·007	0·007	0·008	0·009	—

by rearrangement of the alcohol produced in the reaction, autocatalysed by the developing acid. Certainly the amount formed towards the beginning of the reaction is negligibly small, and represents less than 1% of the total reaction.

(d) *Reactions of* 3 : 3-*Dichloroprop*-1-*ene and* trans-1 : 3-*Dichloropropene in Anhydrous Formic Acid.*—The ratio [acraldehyde derivatives]/[chloride] was followed in anhydrous formic acid at 100° in a similar manner. Any interference by the formic acid with the measurements of acraldehyde was allowed for by estimating standard samples of acraldehyde in the presence of formic acid at the same time. With *trans*-1 : 3-dichloropropene, the production of acraldehyde was autocatalytic in the absence of formate ions, but followed the development of chloride closely when formate ion was added. It is presumed that the function of added formate was to inhibit the acid-catalysed rearrangement of the formate produced in the solvolysis; it was shown in a separate experiment that 1-chloro-3-hydroxyprop-1-ene rearranges rapidly in the absence of formate ions in formic acid at 100°, but that liberation of chloride is almost completely inhibited by the addition of 0·016M-sodium formate. The following data illustrate the constancy of the [derivatives of acraldehyde]/[chloride] ratio, in the reaction of *trans*-1 : 3-dichloropropene in anhydrous formic acid with added 0·0233M-sodium formate at 100°, determined as in (c) above.

Time (min.)	0	7	14	21·5	28	35	42	49	56	∞
Chloride (ml. 0·01N-$AgNO_3$)	3·50	4·75	5·98	7·20	8·30	9·48	10·67	11·60	12·60	167·8
Derivs. of acraldehyde (arbitrary Spekker reading)	0·045	0·092	0·138	0·185	0·231	0·279	0·323	0·364	0·415	—
[Derivs. of acraldehyde]/[chloride]	—	0·085	0·085	0·085	0·088	0·088	0·087	0·089	0·091	—

With either 0·0429N- or 0·0621N-sodium formate the corresponding ratio was 0·085.

Under similar conditions, 3 : 3-dichloroprop-1-ene consistently gave higher ratios of [acraldehyde derivatives]/[chloride] (*ca.* 0·20; cf., in 50% ethanol, 0·18; cf. also de la Mare and Vernon, *Research*, 1953, **6**, 56S).

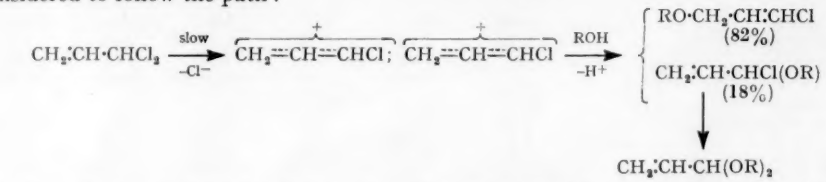
(e) *Reaction of* trans-1 : 3-*Dichloropropene with Aqueous Cuprous Chloride in Acid Solution.*—Cuprous chloride (0·5 g.) was heated with 0·1N-hydrochloric acid (200 ml.) in a current of nitrogen. The solution was filtered, and an aliquot part (100 ml.) was sealed with 6·145 g. of *trans*-1 : 3-dichloropropene and kept for 2 weeks at 45°, with occasional shaking. An aliquot part (20 ml.) of the solution, in which most of the chloride had solvolysed, was added to excess of 2 : 4-dinitrophenylhydrazine (0·1% in 2N-HCl). The precipitate was collected by filtration and weighed 0·082 g. This recovery represents an [acraldehyde]/[chloride] ratio for the total solvolysis of 0·04. After a further 2 weeks at 45°, another aliquot part, treated similarly, gave 0·081 g. of acraldehyde 2 : 4-dinitrophenylhydrazone.

(f) *Reactions of* 1 : 1 : 1-*Trichloro*-2-*methylprop*-1-*ene with Thiophenoxide Ions in Ethanol–Water Mixtures.*—To confirm that the S_N2' reaction is somewhat increased in rate by an increase in the ionising power of the solvent, the reactions of 1 : 1 : 1-trichloro-2-methylprop-1-ene with sodium thiophenoxide was studied at 25° in 90% and in 75% ethanol. The results, given in the discussion, are second-order rate coefficients, calculated from the weight of chloride taken, on the basis that one chlorine atom is released in the reaction. These values were constant within experimental error over the 75% of the reaction studied.

Discussion

(a) *Unimolecular Solvolysis of* 3 : 3-*Dichloroprop*-1-*ene.*—In 50% ethanol, the solvolysis of 3 : 3-dichloroprop-1-ene is clearly unimolecular, since the rate of reaction is but little accelerated by the addition of alkali to the solvent. Under these conditions, release of chloride shows that 82% of rearranged products ($CHCl{:}CH{\cdot}CH_2{\cdot}OR$; R = OH, OEt) are produced. Derivatives of acraldehyde can be obtained from the products, and, since

these do not themselves rearrange under the conditions of the measurements, the reaction is considered to follow the path:



Kirrmann, Schmitz, and Saito's conclusion (*loc. cit.*) that this particular solvolysis is unimolecular, is therefore correct, but it was reached by the incorrect reasoning that the reaction involves complete allylic shift; in fact, both unrearranged and rearranged products are obtained, as is the common experience in anionotropic systems. It should be noted that the proportion of rearrangement (82%) differs considerably from that observed under bimolecular conditions, either in ethanol (with OEt^-, *ca.* 40%; cf. Part I; with SPh^-, 38%; cf. Part II); or in aqueous ethanol (with SPh^-, 28%; cf. this paper).

(b) *Unimolecular Solvolysis of* trans-1 : 3-*Dichloropropene.*—To obtain a substantially unimolecular solvolysis of this compound, it has been necessary to work in anhydrous formic acid. Here the reaction cannot be followed to completion seeing that it is reversible, and also because the solvent slowly decomposes (cf. Part V, *loc. cit.*). When rearrangement of the products of solvolysis is minimised by the addition of sodium formate (which does not affect the rate of production of chloride ion), the ratio [acraldehyde derivatives]/[chloride] is substantially constant, and corresponds with the liberation of 54% of the chlorine from the organic chloride (*i.e.*, *ca.* 8% rearrangement).* It is to be noted that this result disagrees with Hatch, Morgan, and Tweedie's opinion (*J. Amer. Chem. Soc.*, 1952, **74**, 1826). They examined the solvolysis, in water, catalysed by cuprous chloride, of the 1 : 3-dichloropropenes, and showed by tracer methods, using ^{36}Cl, that the vinylic chlorine of the dichloride is partly removed in the reaction, and that the $CHCl{:}CH{\cdot}CH_2{\cdot}OH$ formed as product becomes partly labelled with ^{36}Cl. They proposed a scheme (their Fig. 2, *loc. cit.*, p. 1827) of the S_N1' type, involving a mesomeric cation, $CHCl{:}CH{\cdot}\overset{+}{C}H_2 \longleftrightarrow \overset{+}{C}HCl{\cdot}CH{:}CH_2$. This they regard as reacting reversibly with ^{36}Cl to form $^{36}Cl{\cdot}CHCl{\cdot}CH{:}CH_2$, thus partly labelling the organic chloro-alcohol.† Any significant reaction by the proposed route would, however, result in the liberation of more than 50% of the organic chlorine as chloride ions, with the consequent formation of derivatives of acraldehyde. They regard the latter possibility as excluded by their experimental finding that only 50% of chlorine is released as chloride; we, on the other hand, regard this observation as inconsistent with their tracer experiments and with their explanation of the course of the reaction, since both 3 : 3-dichloroprop-1-ene and 1 : 3-dichloropropene in our experience form derivatives of acraldehyde when solvolysed by S_N1 reactions.

Although we have not examined in detail the hydrolysis catalysed by cuprous chloride, since this reaction may be mechanistically complicated and not adequately represented by the S_N1 mechanism, the solvolysis of *trans*-1 : 3-dichloropropene in the presence of cuprous chloride has been repeated. Our experience is that, when the solvolysis has been allowed to proceed nearly to completion at 45° in a sealed tube, the solution contains acraldehyde, identifiable as its 2 : 4-dinitrophenylhydrazone, in amount consistent with the occurrence of the S_N2 and S_N1' reactions, each contributing equally, assuming that, as in formic acid, reaction of this compound by the latter mechanism gives a ratio of [acraldehyde]/[chloride] of *ca.* 0·08. The products on further standing under the conditions of the reaction released no additional acraldehyde, and hence it is concluded that acraldehyde is a genuine product of the solvolysis, and not a product of rearrangement of the chloro-alcohol produced as the other main organic product.

(c) *Bimolecular Solvolysis of* trans-1 : 3-*Dichloropropene.*—Kirrmann, Schmitz, and

* The fact that this ratio is different from that found with 3 : 3-dichloroprop-1-ene has been discussed elsewhere (de la Mare and Vernon, *loc. cit.*; cf. de la Mare, *Ann. Reports*, 1953, **50**, 139) and will be the subject of a future communication.

† They do not, however, exclude that the labelling might be introduced in a bimolecular process.

Saito (*loc. cit.*) concluded that the solvolysis of this compound, in aqueous alcohol or in aqueous dioxan, was probably unimolecular. In our view, this conclusion is incorrect. The reaction in aqueous ethanol releases, within experimental error, 50% of the chlorine from the compounds as chloride ion, and results in the formation of less than 1% of derivatives of acraldehyde. If the reaction proceeded through a mesomeric cation, it would be expected that there would be produced, as there is in anhydrous formic acid, some 8% of derivatives of acraldehyde by rearrangement.

The following Table shows the effect of added alkali on the rate of liberation of acid from the 1 : 3-dichloropropenes in ethanol and in mixtures of ethanol and water.

The bimolecular solvolyses (first half of Table) are strongly accelerated by increase in the ionising power of the solvent, in agreement with Hughes and Ingold's theory (*J.*, 1935, 252) for a reaction, such as this, in which two neutral molecules react, producing a transition state in which charges develop. The change in rate, on going from ethanol to 50% ethanol, involves a rate-factor of about 40. This may be contrasted, first, with the much greater increase observed for similar solvent changes in unimolecular processes (a factor of about

Solvent effect on the bimolecular reactions of the 1 : 3-*dichloropropenes at* 44·6°.

1 : 3-Dichloropropene	10^5k_1 (min.$^{-1}$) for solvolysis in :			10^5k_2 (l. mole^{-1} min.$^{-1}$) with added OR^- = 0·16M in :		
	EtOH	75% EtOH	50% EtOH	EtOH	75% EtOH	50% EtOH
trans-	0·23	3·3	9·9	3100	2620	2560
cis-	0·22	3·1	9·9	2690	2930	3520

4000; cf. Part VI, *loc. cit.*, for a typical example). Such a difference would be expected, seeing that, in the latter reaction charge-development in the transition state is likely to be greater, and will be spread over a smaller volume. Secondly, comparison may be made with a bimolecular displacement of an anion on a neutral molecule (cf. second half of Table). In this case, a large change in solvent results in only a small change in rate; in the present example, one of the compounds shows a small decrease, and the other a small increase, when the ionising power of the solvent is increased. These results are in substantial agreement with those of Andrews and Kepner (*J. Amer. Chem. Soc.*, 1948, **70**, 3456).

The consequence of the difference in behaviour when the solvent is changed, between the bimolecular solvolysis and the bimolecular reaction with alkali, is that the acceleration in rate of a bimolecular solvolysis when a given amount of alkali is added, is reduced when water is added to the alcoholic solvent, by a factor of about 40 on going from ethanol to 50% ethanol. The present results establish the situation for a case in which the solvolytic reaction can be proved to be substantially bimolecular, and hence can be used as a guide in other cases, as will be discussed by one of us in a later paper.

(d) *Solvent Effects in the* S_N2' *Reaction.*—In a previous paper (Part VI, *loc. cit.*), it was argued on general grounds that the effect of change of solvent on the rate of an S_N2' reaction would not be likely to be large, since other bimolecular processes involving ions and neutral molecules are usually not much affected by such changes. It is desirable, however, to have definite information on this point, and so we have examined the reaction of 3 : 3 : 3-trichloro-2-methylprop-1-ene with sodium thiophenoxide in ethanol–water mixtures, with the following results: 3 : 3 : 3-trichloro-2-methylprop-1-ene + SPh^- at 25·0°; k_2 (l. mole^{-1} min.$^{-1}$), $6{\cdot}5 \times 10^{-3}$ in ethanol (Part III, *loc. cit.*); $8{\cdot}2 \times 10^{-3}$ in 90% ethanol; $13{\cdot}0 \times 10^{-3}$ in 75% ethanol. Similarly, 3 : 3-dichloroprop-1-ene reacts in 75% ethanol with SPh^- at 45·7° to release 86% of its chlorine as chloride, and with rate coefficient, based on this release of chloride, $k_2 = 0{\cdot}190$ l. mole^{-1} min.$^{-1}$. Comparison with the results given in Part II for reactions in ethanol (total k_2, 0·064 l. mole^{-1} min.$^{-1}$ at 45·2°; 81% chlorine released at infinity) shows that both S_N2 and S_N2' processes have been accelerated by increase in the ionising power of the solvent, and the former process is accelerated rather more than the latter.

We thank Mr. T. Collins for technical assistance. We are indebted to Professors E. D. Hughes, F.R.S., and C. K. Ingold, F.R.S., for their continued encouragement and interest.

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University College, London, W.C.1. [*Received, May 7th*, 1954.]

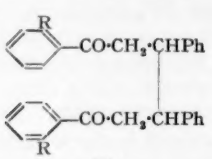
The Structure of Tannins. Part II. The Reduction Products of 2′-Hydroxy- and 2′-Methoxy-chalkones and of Flavanone.*

By James Jack, J. C. Watkins, and D. E. White.

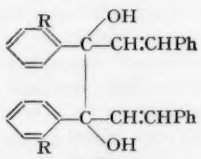
[Reprint Order No. 5401.]

The course of reduction of 2′-hydroxy- and 2′-methoxy-chalkones † with zinc and acetic acid resembles closely that of chalkone (Part I *). The main products are (±)- and *meso*-1 : 6-di-*o*-hydroxyphenyl-3 : 4-diphenylhexane-1 : 6-diones (I; R = OH) and their methyl ethers (I; R = OMe), respectively. The *meso*-dione (I; R = OH) is shown to differ from the pinacol (III) of similar m. p. formed by reduction of flavanone.

In Part I * of this series it was shown that the reduction products obtained from chalkone with zinc dust and acetic acid were *meso*- and (±)-1 : 3 : 4 : 6-tetraphenylhexane-1 : 6-diones (I; R = H), neither isomer having the pinacol structure (II; R = H) suggested for the lower-melting compound by Russell and Todd (*J.*, 1934, 1066). The possibility that 2′-hydroxychalkone might yield a "flavpinacol" (III) remained, however, since it could cyclise to flavanone before reduction, and previous investigators (Freudenberg and Orthner, *Ber.*, 1922, **55**, 1748; Geissman and Clinton, *J. Amer. Chem. Soc.*, 1946, **68**, 700) had obtained the pinacol (III) by reduction of flavanone. Furthermore, Russell (*J.*, 1934, 218) observed that the reduction products of 2′-hydroxychalkones were insoluble in alkali, in agreement with the structure (III).



(I)



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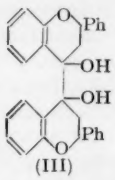

(III)

In order to obtain reference compounds, the reduction of 2′-methoxychalkone was first studied and, from the mixture of products, *meso*- and (±)-1 : 6-di-*o*-methoxyphenyl-3 : 4-diphenylhexane-1 : 6-dione (I; R = OMe) were isolated and characterised as oximes. Confirmation of the structure of the *meso*-isomer was obtained by its synthesis from di-*o*-methoxyphenylcadmium and *meso*-ββ′-diphenyladipoyl chloride. This reaction also yielded a compound, $C_{32}H_{28}O_3$, m. p. 224°, which is presumably a dehydration product of the *meso*-dione, but is not identical with *cis*-1-*o*-methoxybenzoyl-2-*o*-methoxyphenyl-4 : 5-diphenyl*cyclo*pentene, obtained by treatment of the *meso*-dione with alcoholic hydrochloric acid.

Condensation of (±)-ββ′-diphenyladipoyl chloride with di-*o*-methoxyphenylcadmium did not yield a crystalline product but acid treatment of the crude product afforded *trans*-1-*o*-methoxybenzoyl-2-*o*-methoxyphenyl-4 : 5-diphenyl*cyclo*pentene, identical with the dehydration product obtained from the (±)-dione (I; R = OMe).

The reduction of 2′-hydroxychalkone yielded three compounds. Two of these were identified as the *meso*- and (±)-1 : 6-di-*o*-hydroxyphenyl-3 : 4-diphenylhexan-1 : 6-diones (I; R = OH) respectively by methylation to the two diones (I; R = OMe) described above. The (±)-isomer was readily soluble in aqueous alkali and gave a strong ferric reaction; but the *meso*-isomer was not soluble in aqueous alkali and gave no ferric reaction, although it dissolved on addition of alkali to its suspension in acetone or methanol. Possibly Russell's alkali-insoluble reduction products were similar "cryptophenolic" compounds.

* Part I, *J.*, 1950, 3367.

† For numbering see Editorial Report on Nomenclature, *J.*, 1953, 4201.

The constitution of the third reduction product, $C_{30}H_{24}O_3$, m. p. 144°, is uncertain since pure derivatives have not been obtained from it, but it is probably an *o*-hydroxybenzoyl-*o*-hydroxyphenyldiphenyl*cyclo*pentene. It has a strongly hydrogen-bonded and conjugated carbonyl group (infra-red absorption at 1644 cm.$^{-1}$ in a mull, 1642 cm.$^{-1}$ in chloroform) and also shows the broad hydroxyl absorption (*ca.* 3300 cm.$^{-1}$) characteristic of hydrogen bonding.

The *meso*-dione (I; R = OH) has a melting point very close to that of flavpinacol (III) described by Freudenberg and Orthner and by Geissman and Clinton (*locc. cit.*). However, comparison of the properties of these compounds, shown together with those of the (±)-dione (I; R = OH) in the Table, indicates that the structures assigned to them are correct. A mixed melting point also showed a considerable depression.

Reduction products of flavanone and 2′-hydroxychalkone.

Compound	Solution in H_2SO_4	Ultra-violet absorption (in EtOH) $\lambda_{max.}$ (mμ) (log ε)	Infra-red absorption (cm.$^{-1}$)	M. p.
Flavpinacol (III)	Red	279 (3·76); 285 (3·75)	No CO band; 3500 (OH)	255—256°
meso-Dione (I; R = OH)	Greenish-yellow	254 (4·35); 328 (3·94)	1637 (CO) *	256—257°
(±)-Dione (I; R = OH)	Greenish-yellow	254 (4·29); 328 (3·9)	1634 (CO) *	126°

* No sharp OH band (H-bonded).

Thus it is clear that reduction of 2′-hydroxychalkone with zinc and acetic acid resembles closely that of chalkone (Part I) in forming bimolecular diketones. This is normal with αβ-unsaturated ketones (Kohler and Thompson, *J. Amer. Chem. Soc.*, 1937, **59**, 887) but, on the other hand, flavpinacol is a normal product of the reduction of the saturated aromatic ketone, flavanone.

So far we have no positive evidence of the interconversion of 2′-hydroxychalkone and flavanone during the reduction with zinc and acetic acid, although Geissman and Clinton (*loc. cit.*) found such interconversion during reductions with sodium amalgam and with magnesium and hydrochloric acid. Thus we cannot be certain that Russell's tannin-like compounds did not contain "flavpinacols," but it seems certain that they must have contained considerable quantities of the bimolecular diketones. Consequently deductions of tannin structure based on other assumed constitutions lack firm foundation.

Experimental

M. p.s are corrected. Some of the analyses are by Dr. Zimmerman, C.S.I.R.O., Melbourne.

Reduction of 2′-Methoxychalkone.—Zinc dust (100 g.) was added in small portions during 1 hr. to a refluxing solution of 2′-methoxychalkone (25 g.; b. p. 226°/11 mm.) in alcohol (500 ml.) and acetic acid (75 ml.), and refluxing was continued for 15 min. When the filtered solution was cooled for 2 hr. at 0°, crystals (A; 12 g.) separated. After a further 18 hr. at 0° a second crop (B; 2·8 g.) was obtained. On concentration to 200 ml. a third (C; 1·3 g.) and after 2 days at 0° a fourth crop (D; 0·75 g.) crystallised.

Fractions B and D, after being washed with water to remove zinc acetate, formed hexagonal plates of (±)-1 : 6-*di*-o-*methoxyphenyl*-3 : 4-*diphenylhexane*-1 : 6-*dione* (2·5 g.), m. p. 177—178°, from methanol [Found: C, 80·3; H, 6·6; OMe, 12·9%; *M* (Rast), 550. $C_{32}H_{30}O_4$ requires C, 80·3; H, 6·3; 2OMe, 13·0%; *M*, 478·6]. With hydroxylamine hydrochloride and pyridine (cf. Part I) it formed a *dioxime*, prisms, m. p. 228°, from aqueous acetic acid (Found: C, 75·5; H, 6·1; N, 5·7. $C_{32}H_{32}O_4N_2$ requires C, 75·6; H, 6·3; N, 5·5%).

Fractions A and C, after removal of zinc acetate with boiling water, yielded meso-1 : 6-*di*-o-*methoxyphenyl*-3 : 4-*diphenylhexane*-1 : 6-*dione* (2·5 g.), m. p. 197—198°, in the less soluble fractions from methanol [Found: C, 80·7; H, 6·1; OMe, 12·4%; *M* (Rast), 360] and a further crop (0·4 g.) of the (±)-isomer from the more soluble fractions. The *meso*-isomer formed a *dioxime*, rectangular plates, m. p. 262° from methanol–pyridine (20 : 1) (Found: C, 75·7; H, 6·4; N, 5·3%).

Both diones were stable to bromine in carbon tetrachloride and to permanganate in acetone.

meso-1 : 6-*Di*-o-*methoxyphenyl*-3 : 4-*diphenylhexane*-1 : 6-*dione*.—To the Grignard reagent prepared from *o*-bromoanisole (2 g.), ether (12·5 ml.), and magnesium turnings (0·25 g.), dry cadmium chloride (1·4 g.) was added during 90 min., with stirring. Thirty minutes later a solution of *meso*-ββ′-diphenyladipoyl chloride (0·3 g.) in warm benzene was added and after removal of the ether the mixture was stirred while refluxing for 2 hr. Ice and dilute hydrochloric acid were added and the mixture was distilled with steam. 2 : 2′-Dimethoxydiphenyl, m. p. 155°, separated from the distillate and a resinous solid (0·4 g.) from the residue. After extraction of the latter with ether, the residue (70 mg.) formed crystals, m. p. 224°, from chloroform–ethanol (1 : 4) (Found : C, 83·6; H, 6·6. $C_{32}H_{28}O_3$ requires C, 83·5; H, 6·1%). The ether-soluble material was chromatographed on alumina (activity IV), and from the light petroleum–benzene (1 : 2) eluate prisms of *meso*-1 : 6-di-*o*-methoxyphenyl-3 : 4-diphenylhexane-1 : 6-dione separated, having m. p. 194—195° raised to 196—197° on admixture with the reduction product (m. p. 197°) of 2′-methoxychalkone.

trans-1-o-*Methoxybenzoyl*-2-o-*methoxyphenyl*-4 : 5-*diphenyl*cyclo*pentene*.—(±)-1 : 6-Di-*o*-methoxyphenyl-3 : 4-diphenylhexane-1 : 6-dione (0·2 g.) was dissolved in boiling methanol, and hydrochloric acid was added to faint turbidity and then enough methanol to form a clear solution, which was refluxed for 2 hr. trans-1-o-*Methoxybenzoyl*-2-o-*methoxyphenyl*-4 : 5-*diphenyl*cyclo*pentene* (40 mg.) separated from the hot solution and a further 120 mg. on cooling. It formed hexagonal plates, m. p. 148—149°, from chloroform–methanol [Found : C, 82·9; 83·0; H, 6·2, 6·1; OMe, 13·6; *M* (Rast), 429, 449. $C_{32}H_{28}O_3$ requires C, 83·4; H, 6·1; 2OMe, 13·5%; *M*, 460·5].

The same compound (m. p. and mixed m. p.) was obtained from the reaction between di-*o*-methoxyphenylcadmium and (±)-ββ′-diphenyladipoyl chloride, followed by treatment of the amorphous non-volatile product with alcoholic hydrogen chloride. It decolorises bromine in carbon tetrachloride quite rapidly.

cis-1-o-*Methoxybenzoyl*-2-o-*methoxyphenyl*-4 : 5-*diphenyl*cyclo*pentene*.—The *meso*-dione (0·2 g.), treated with alcoholic hydrogen chloride, yielded cis-1-o-*methoxybenzoyl*-2-o-*methoxyphenyl*-4 : 5-*diphenyl*cyclo*pentene* (0·1 g.) which formed prisms, m. p. 155°, from methanol [Found : C, 83·4; H, 6·2%; *M* (Rast), 328] and decolorised bromine in carbon tetrachloride.

Reduction of 2′-*Hydroxychalkone*.—2′-Hydroxychalkone (15 g.) was reduced by the method described for 2′-methoxychalkone. The mixture was poured into water and extracted with ether and the ethereal solution extracted with 5% aqueous sodium hydroxide. Acidification of the alkaline solution yielded (±)-1 : 6-*di*-o-*hydroxyphenyl*-3 : 4-*diphenylhexane*-1 : 6-*dione* (3·15 g.) which formed long hexagonal plates, m. p. 126°, from chloroform–methanol [Found : C, 80·4, 80·2; H, 5·7, 5·9%; *M* (Rast), 422, 413. $C_{30}H_{26}O_4$ requires C, 80·0; H, 5·8%; *M*, 450·5]. It gave a red colour with ferric chloride but did not decolorise bromine in carbon tetrachloride and reacted only very slowly with permanganate in acetone. On methylation with methyl sulphate and sodium hydroxide in aqueous-methanolic acetone it formed (±)-1 : 6-di-*o*-methoxyphenyl-3 : 4-diphenylhexane-1 : 6-dione, identical (m. p. and mixed m. p.) with the material described above.

Treatment of (±)-1 : 6-di-*o*-hydroxyphenyl-3 : 4-diphenylhexane-1 : 6-dione with acetic anhydride and pyridine afforded the *diacetate*, fine needles, m. p. 144°, from 95% ethanol (Found : C, 76·6; H, 5·9. $C_{34}H_{30}O_6$ requires C, 76·4; H, 5·7%). It showed carbonyl absorption bands at 1760 and 1697 cm.$^{-1}$.

The ethereal solution yielded a product (1·6 g.), which formed short rods, m. p. 144°, from chloroform–methanol [Found : C, 83·2, 83·4; H, 5·6, 5·5; active H, 0·39%; *M* (Rast), 449, 463. Calc. for $C_{30}H_{24}O_3$: C, 83·3; H, 5·6; 2 active H, 0·47%; *M*, 432·5]. It gave a brown ferric reaction and reacted rapidly with bromine and with permanganate.

The insoluble residue, after removal of zinc acetate with hot water, was extracted continuously for 10 hr. with boiling benzene. From the cooled extract, meso-1 : 6-*di*-o-*hydroxyphenyl*-3 : 4-*diphenylhexane*-1 : 6-*dione* (3·75 g.) separated; this formed long prisms, m. p. 256—257°, from methylene chloride–methanol [Found : C, 79·9; H, 6·1%; *M* (Rast), 560]. A further crop (0·2 g.) was obtained on concentration of the benzene extract. It was sparingly soluble in methanol, ethanol, acetone, and benzene but on addition of potassium hydroxide to a suspension in methanol or acetone it dissolved readily. It gave no ferric reaction.

On acetylation with acetic anhydride and pyridine at the b. p. for 15 min. it yielded a *diacetate*, which formed needles, m. p. 241—242°, from chloroform–methanol (Found : C, 76·3; H, 5·55%). This showed carbonyl bands at 1745 and 1686 cm.$^{-1}$, characteristic of the acetate-carbonyl and the carbonyl attached to a benzene ring, respectively.

On methylation with methyl sulphate and potassium hydroxide in acetone *meso*-1 : 6-di-*o*-

methoxyphenyl-3 : 4-diphenylhexane-1 : 6-dione was obtained, having m. p. 196—196·5° undepressed on admixture with the reduction product (m. p. 197—198°) of 2′-methoxychalkone.

The authors are indebted to Dr. A. R. H. Cole and Dr. R. N. Hazeldine for the infra-red spectra and to the Ramsay Memorial Fellowship Trust for a fellowship (to J. J.).

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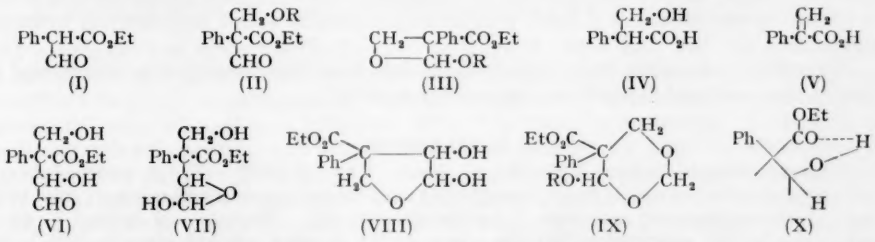
The Reaction between Formaldehyde and Ethyl α-Formylphenylacetate.

By C. A. FRIEDMANN and J. M. Z. GLADYCH.

[Reprint Order No. 5442.]

Re-examination has shown that the above reaction gives considerable amounts of 5-ethoxycarbonyl-4-hydroxy-5-phenyl-1 : 3-dioxan (IX; R = H).

INVESTIGATION of the action of aqueous formaldehyde (35%) on ethyl α-formylphenylacetate (I) led Gault and Cogan (*Bull. Soc. chim.*, 1941, **8**, 140) to conclude that the product was substantially ethyl α-formyltropate (II; R = H) or the oxetan (III; R = H). They attributed the low carbon analyses to inadequate removal of moisture and the presence of some polyoxymethylenes, but based their structural conclusions mainly on the chemical behaviour of the product. Thus the product afforded a silver mirror in the cold, and gave a positive Schiff's test (aldehyde). It readily regenerated formaldehyde and ethyl α-formylphenylacetate, and gave a crystalline monoacetate which gave carbon and hydrogen analyses consistent with structure (II or III; R = Ac). In addition, hydrolysis with barium or sodium hydroxide afforded mixtures of tropic (IV), atropic (V), and phenylacetic acid.



In a reinvestigation in these laboratories the product afforded a crystalline fraction in yields of up to 50% (crude), analyses of which accorded with the empirical formula $C_{13}H_{16}O_5$, *i.e.*, (II; R = H) $+CH_2O$. This substance gave a silver mirror in the cold, readily lost formaldehyde at the melting point with reversion to (I), and afforded a crystalline monoacetate. Reduction could not be effected catalytically (palladium–charcoal or Adams catalyst) or with lithium aluminium hydride in tetrahydrofuran (reverse addition), and sodium borohydride gave boron complexes which could not be split. Hydrolysis with aqueous barium hydroxide gave tropic acid.

Structures (VI), (VII), and (VIII) were excluded by formation of only a monoacetate, because the resistance to reduction contraindicates an aldehyde group, and by infra-red spectral measurements. Structure (IX), however, accords with the facts. 4-Hydroxy-1 : 3-dioxans are known to arise by the action of aldehydes on aldols (Späth, Lorentz, and Freund, *Ber.*, 1944, **77**, 354; Späth, Lorentz, and Altman, *Ber.*, 1943, **76**, 513; Saunders and Murray, *J. Amer. Chem. Soc.*, 1944, **66**, 206) and to lose formaldehyde under mild conditions. The C–OH stretching frequency due to the hydroxyl group of ethyl tropate (cf. IV) (primary alcohol) appeared at 1040 cm.$^{-1}$ (see Table); the corresponding band in the new substance had been displaced to 1080 cm.$^{-1}$, which is compatible with a secondary hydroxyl group (Zeiss and Tsutsui, *ibid.*, 1953, **75**, 897). If, as this suggests,

there is no primary alcoholic group present, the substance, m. p. 109°, must possess a cyclic structure. In the C=O stretching region in chloroform solutions the only band is that of the ester-carbonyl group at 1730 cm.$^{-1}$; there can thus be no free aldehyde group. It is interesting that in Nujol mull the ester-carbonyl frequency is displaced to 1715 cm.$^{-1}$; this might arise as a result of hydrogen bonding in the crystal lattice, which could be facilitated by a spatial arrangement such as (X). The wide hydroxyl band in the 3300-cm.$^{-1}$ region provides strong support for hydrogen bonding, which is further substantiated by the fact that ethyl α-formylphenylacetate and ethyl tropate have one large band at 1175 cm.$^{-1}$, whereas the new compound has three bands (1192, 1185, and 1164 cm.$^{-1}$). This type of resolution of the ester band has been attributed by Mazur and

Main infra-red absorption peaks (cm.$^{-1}$). (*In Nujol, except where stated.*)

	OH	CO			Ester		OH	
(IX; R = H)	*ca.* 3300	1715	—	1265	1192	—	1080	998
	—	—	—	1245	1185	—	—	980
	—	—	—	—	1164	1135	—	925
	—	—	—	—	—	—	—	902
	—	1730	(in $CHCl_3$)	—	—	—	—	—
(I)	—	1717	1400	1275	1175	1155	—	1020
	—	(1653 enol)	1380	—		—	—	—
	—	—	1340	—	—	—	—	—
Ethyl tropate (cf. IV)	—	1727	1595	1260	1175	—	1040	1025
	—	—	1490	—	—	—	—	—
	—	—	1453	—	—	—	—	—
	—	—	1380	—	—	—	—	—
	—	—	1346	—	—	—	—	—
Tetrahydro-3 : 4-dihydroxy-	—	—	—	—	—	1130	1098	1020
2 : 5-dimethoxyfuran	—	—	—	—	—	—	—	990
	—	—	—	—	—	—	—	980
	—	—	—	—	—	—	—	953
	—	—	—	—	—	—	—	940

Spring (*J.*, 1954, 1224) to the presence of a relatively hindered ester group, such as might be present in our substance if there were hydrogen bonding with a neighbouring hydroxyl group.

Attempts to isolate a pure, oily product, free from the dioxan, were abandoned in view of the continued deposition of crystalline material.

Experimental

5-Ethoxycarbonyl-4-hydroxy-5-phenyl-1 : 3-dioxan (IX; R = H).—Ethyl α-formylphenylacetate (40·4 g.) in benzene (120 c.c.) was treated with formaldehyde solution (48 g.; 36—40%) and anhydrous potassium carbonate (1·2 g.) in water (2 c.c.). Benzene was omitted by Gault and Cogan in this preparation, but the course of the reaction was the same in both cases. The mixture was left overnight, and the benzene layer then separated, washed with a little water, and dried (Na_2SO_4). After removal of the solvent at 20—30° under reduced pressure, the residual oil partly crystallized. The crystals (20 g.; m. p. 89—90°) were collected and dried in a vacuum-desiccator (P_2O_5). These dissolved almost completely in dry ether. The solution was filtered and treated with light petroleum (b. p. 40—60°). The precipitated *dioxan* was recrystallized from the same solvent mixture, being obtained as colourless scales, m. p. 109° (Found: C, 61·9; H, 6·4. $C_{13}H_{16}O_5$ requires C, 61·9; H, 6·35%), insoluble in cold water and melting in hot water. It was soluble in ethanol, ether, sparingly soluble in benzene, insoluble in light petroleum. It gave no colour with ferric chloride solution, but reduced ammoniacal silver nitrate solution at room temperature, and Fehling's solution on warming. After having been boiled in aqueous alcohol for a few minutes, the product yielded a violet colour with ferric chloride, identical with that given by ethyl α-formylphenylacetate under analogous conditions. The solid, when heated at, or above, its m. p. evolved formaldehyde; the residual oil gave a violet colour with ferric chloride solution and was identified as ethyl α-formylphenylacetate, b. p. 95—96°/2 mm., n_D^{20} 1·5170.

The dioxan (0·1 g.) was dissolved in a solution of dimedone (0·3 g.) in magnesium-dried ethanol (4 c.c.). No crystallization occurred during several days. The clear solution was then diluted with water. The crystals which appeared overnight were the formaldehyde–dimedone complex, m. p. and mixed m. p. 188—189°.

Alkaline Hydrolysis.—The dioxan (IX; R = H) (2·5 g.) was stirred with barium hydroxide octahydrate (4 g) in water (10 c.c.), formaldehyde being liberated in a few minutes. After 2·5 hr. the solid was filtered off, suspended in water (3 c.c.), and acidified (Congo-red) The precipitated tropic acid, recrystallized from water, had m. p. and mixed m. p. 116—117° (0·79 g.).

Acetylation.—The dioxan (2·5 g.) was kept in dry pyridine (18 c.c.) with acetic anhydride (3 c.c.) for 15 hr. at 20°. The mixture was poured into ice-water, and the crude *acetate*, which slowly crystallized (2·3 g.), was recrystallized from light petroleum (b. p. 40—60°), affording colourless prisms, m. p. 76—77° (Found: C, 61·0; H, 6·0. $C_{15}H_{18}O_6$ requires C, 61·1; H, 6·1%).

The acetate (0·3 g.) was recovered unchanged after being kept in a solution of dimedone (0·4 g.) in magnesium-dried ethanol (4 c.c.) for several days.

We thank Professor Clemo, F.R.S., for his continued interest, Messrs. R. G. J. Miller and H. A. Willis of Imperial Chemical Industries Limited, Plastics Division, for the spectral measurements and discussion on their interpretation, and the Directors of Messrs. Carnegies of Welwyn Limited for permission to publish this work.

CARNEGIES OF WELWYN LIMITED, WELWYN GARDEN CITY, HERTS. [*Received, June 4th*, 1954.]

Triterpenoids. Part XIX. The Constitution of Lantadene B.*

By (*a*) D. H. R. BARTON, P. de MAYO, and E. W. WARNHOFF, and (*b*) O. JEGER and G. W. PEROLD.†

[Reprint Order No. 5463.]

Lantadene B has been shown to have the composition $C_{35}H_{52}O_5$. On alkaline hydrolysis it affords ββ-dimethylacrylic acid and 22β-hydroxyoleanonic acid. On the basis of this and other evidence lantadene B is shown to be 22β-(ββ-dimethylacryloyloxy)oleanonic acid.

IN previous parts of this series (Barton and de Mayo, *J.*, 1954, 887, 900) the constitution of icterogenin, the photosensitivity-conferring constituent of *Lippia rehmanni* Pears, was elucidated as (I; R = angeloyloxy), and the occurrence of a further triterpenoid acid, rehmannic acid (II; R = angeloyloxy, R′ = H), was demonstrated. Substances of obviously related chemical constitution have been isolated by Louw (*Onderstepoort J. Vet. Sci.*, **1943**, **18**, 197; 1948, **23**, 233; 1949, **22**, 321, 329) from *Lantana camara* L. and have been designated lantadene A and B. Lantadene A is stated to have the composition $C_{31}H_{44}O_5$ and to be physiologically active in the same way as is icterogenin. Lantadene B on the other hand is regarded as having the composition $C_{33}H_{48}O_5$ and is said to be physiologically inactive. An investigation of the constitutions of the lantadenes was initiated some years ago by two of us (O. J. and G. W. P.) at Zürich. In view of the recently reported work (Barton and de Mayo, *locc. cit.*) on the *Lippia* constituents, and, in particular, having regard to the close resemblance (see below) of lantadene B and rehmannic acid, it was felt desirable to collaborate in the investigation of the chemistry of lantadene B. The current paper describes work on a lantadene mixture isolated at Zürich.

Chromatography of the crude lantadene over silica gel (cf. Barton and de Mayo, *loc. cit.*, p. 887) afforded only one pure substance in good yield. This was shown to be lantadene B by its physical constants, by direct (mixed m. p.) comparison with an authentic specimen of lantadene B very kindly provided by Dr. P. G. J. Louw, and by the identity of infra-red spectra in bromoform solution. Combustion data on lantadene B and its derivatives, and the degradational sequence outlined below, showed that its true molecular formula was $C_{35}H_{52}O_5$, the same as that established (Barton and de Mayo, *loc. cit.*, p. 900) for rehmannic acid. Lantadene B gave an oxime and a 2 : 4-dinitrophenylhydrazone showing, in agreement with Louw (*loc. cit.*), the presence of a carbonyl

* Part XVIII, *J.*, 1954, 2715. † This paper is also to be regarded as Part 178 in the E.T.H. series on Triterpenes. For Part 177 see *Helv. Chim. Acta*, 1953, **36**, 335.

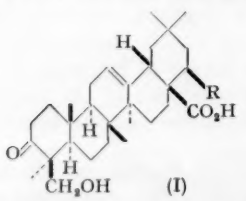
group. The physical constants recorded by us for lantadene B, its oxime, and 2 : 4-dinitrophenylhydrazone are almost identical with those which we reported for rehmannic acid and its derivatives. Lantadene B and rehmannic acid gave a slight melting-point depression on admixture, but the corresponding derivatives did not. The infra-red spectra of the 2 : 4-dinitrophenylhydrazones differed only at three frequencies (1035, 1070, and 1125 cm.$^{-1}$; chloroform solution) in the finger-print region. In the carbonyl region in the infra-red (see Table) rehmannic acid, icterogenin, and lantadene B had identical spectra.

Nevertheless several pieces of experimental evidence contraindicated the identity of lantadene B and rehmannic acid. Lantadene B was an acid affording a methyl ester, but this could not be obtained in the characteristic solvated form of methyl rehmannate. In the ultra-violet region lantadene B showed a maximum at 215 mμ, indicating the presence of an αβ-unsaturated ester grouping as in rehmannic acid ($\lambda_{max.}$ 212 mμ). However lantadene B had a significantly higher absorption (ε 18,000) than rehmannic acid (ε 12,400). The infra-red spectra of lantadene B and of rehmannic acid showed minor, but significant, differences in the finger-print region.

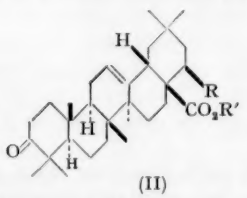
The relation between lantadene B and rehmannic acid was finally revealed by further degradation. On unimolecular ester pyrolysis, lantadene B methyl ester gave ββ-dimethylacrylic acid and a product which, on catalytic hydrogenation, furnished methyl oleanolate, (III). Vigorous alkaline hydrolysis of lantadene B afforded ββ-dimethylacrylic acid

		Infra-red maxima (cm.$^{-1}$)			
		CO_2H	C:O	C:O of C:C·CO·O	C:C of C:C·CO·O
Rehmannic acid (II; R = angeloyloxy, R′ = H)	Nujol	1738	1714	1675	1644
	$CHBr_3$	1752	1710	1710	1652
Icterogenin (I; R = angeloyloxy)	Nujol	1740	1700	1678	1643
Lantadene B (II; R = ββ-dimethylacryloyloxy, R′ = H)	Nujol	1736	1715	1678	1653
	$CHBr_3$	1752	1712	1712	1650

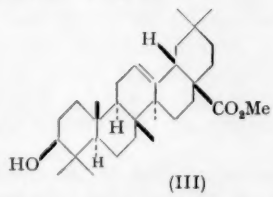
identified as the *p*-bromo- and *p*-phenyl-phenacyl esters, and 22β-hydroxyoleanonic acid (II; R = OH, R′ = H) obtained earlier (Barton and de Mayo, *loc. cit.*, p. 900) by similar hydrolysis of rehmannic acid. The identity of the hydrolysis product was confirmed by its conversion into the methyl ester (II; R = OH, R′ = Me) and by oxidation of the latter to methyl 22-oxo-oleanonate (Barton and de Mayo, *loc. cit.*, p. 900). These degradations, coupled with the ultra-violet absorption spectrum (see above), establish the constitution of lantadene B as 22β-(ββ-dimethylacryloyloxy)oleanonic acid (II; R = ββ-dimethylacryloyloxy, R′ = H). 22β-Hydroxyoleanonic acid has been further characterised by conversion into the dibenzoate of methyl 22β-hydroxyoleanolate.



(I)



(II)



(III)

Louw (*loc. cit.*) has reported that lantadene A affords an acetyl derivative on treatment with acetic anhydride and sodium acetate. Similar reaction of lantadene B has given us the mixed anhydride (II; R = ββ-dimethylacryloyloxy, R′ = Ac), characterised by its ready solvolysis with ethanol back to lantadene B. The infra-red spectrum of the mixed anhydride showed bands (in CS_2 solution) at 1822 and 1755 (mixed anhydride), at 1718 and 1222 (αβ-unsaturated ester), at 1708 (6-ring ketone), and at 1650 cm.$^{-1}$ (C:C conjugated with C:O) in agreement with the assigned constitution.

A more thorough investigation of the acidic constituents of *Lantana camara* L. is in hand in an endeavour to determine the nature of lantadene A.

Experimental

For general experimental conditions see Part VII (*J.*, 1952, 2339). Rotations were determined in $CHCl_3$ solution. Ultra-violet absorption spectra were taken in EtOH solution with the Unicam S.P. 500 Spectrophotometer. Infra-red spectra were kindly determined by Messrs. Glaxo Laboratories. Silica gel for chromatography was obtained from Messrs. Hopkin and Williams Ltd.

Isolation of Crude Lantadene.—The crude lantadene mixture was isolated from a batch of *Lantana camara* leaves exactly as described by Louw (*loc. cit.*). The crude product had m. p. 274—282° (decomp.), $[\alpha]_D$ +82° (*c*, 2·00), $\lambda_{max.}$ 211 mμ (ε 16,900).

Lantadene B.—Chromatography of crude lantadene (4·03 g.) over silica (250 g.) and elution with benzene–ether (19 : 1) gave lantadene B (3·61 g., 90%) in fractions melting between 277° and 290°. Recrystallisation once from benzene–hexane afforded pure *lantadene B*, m. p. 293—294° (decomp.), $[\alpha]_D$ +85° (*c*, 2·40), $\lambda_{max.}$ 214 mμ (ε 18,000) (Found: C, 75·8; H, 9·6. $C_{35}H_{52}O_5$ requires C, 76·05; H, 9·5%), whose physical constants were unchanged on repeated fractional crystallisation and on rechromatography. Authentic lantadene B had m. p. 292—294° (decomp.), undepressed on admixture with the lantadene B described above. *Lantadene B oxime*, prepared in the usual way with pyridine–hydroxylamine hydrochloride, had m. p. (from methanol) 268—269° (decomp.) (Found: C, 74·15; H, 9·45. $C_{35}H_{53}O_5N$ requires C, 74·05; H, 9·4%). *Lantadene B* 2 : 4-*dinitrophenylhydrazone* had m. p. (from chloroform–methanol) 264—265° (Found: C, 66·85; H, 7·65. $C_{41}H_{56}O_8N_4$ requires C, 67·2; H, 7·7%).

Lantadene B Methyl Ester.—Lantadene B (223 mg.) in chloroform (1 ml.) was treated with excess of ethereal diazomethane, and the excess of reagent destroyed with one drop of acetic acid. Chromatography over alumina and elution with benzene gave *lantadene B methyl ester* (174 mg.), m. p. (from hexane) 234—236°, $[\alpha]_D$ +89° (*c*, 2·00) (Found: C, 76·3; H, 9·8. $C_{36}H_{54}O_5$ requires C, 76·3; H, 9·6%).

Treatment of Lantadene B with Acetic Anhydride.—Lantadene B (133 mg.) with anhydrous sodium acetate (500 mg.) and acetic anhydride (3 ml.) was refluxed for 3 hr., cooled, poured into water, and extracted with chloroform. After being washed with sodium hydrogen carbonate solution, the chloroform solution was evaporated *in vacuo* to give the mixed *anhydride* (142 mg.), m. p. 179—189°. Recrystallised from hexane this had m. p. 190—192°, $[\alpha]_D$ +81° (*c*, 1·52) (Found: C, 74·4; H, 9·25. $C_{37}H_{54}O_6$ requires C, 74·7; H, 9·15%). The anhydride (50 mg.) in ethanol (5 ml.) was refluxed for 15 min. Concentration of the solution *in vacuo* gave back lantadene B, m. p. and mixed m. p. 293—294° (decomp.).

Pyrolysis of Lantadene B Methyl Ester.—The methyl ester (169 mg.) was pyrolysed at 550°/0·5 mm. under the conditions used by Barton and de Mayo (*loc. cit.*, p. 887). The acid evolved in the pyrolysis corresponded to 37% elimination. It had m. p. 64—66° and gave marked depressions in m. p. on admixture with both angelic and tiglic acids, but was undepressed in m. p. on admixture with authentic ββ-dimethylacrylic acid of m. p. 69—70°.

The non-acidic product of the pyrolysis was triturated with hexane and the (unchanged) crystalline lantadene B methyl ester was filtered off. The hexane-soluble material (69 mg.) was filtered through alumina in benzene solution, and the eluted product (43 mg.) was hydrogenated in acetic acid over platinum for 12 hr. The hydrogenation product was refluxed with 5% methanolic potassium hydroxide for 20 min. (to hydrolyse any 3β-acetate that had been formed) and the product chromatographed over alumina. Elution with benzene–ether (3 : 1) gave methyl oleanolate (m. p. and mixed m. p.).

Hydrolysis of Lantadene B.—Lantadene B (400 mg., 0·725 mmole) in ethanolic potassium hydroxide (20 ml.; 4%) was refluxed for 6 hr. (cf. Barton and de Mayo, *loc. cit.*, p. 900). After removal of most of the ethanol *in vacuo*, water (20 ml.) was added and sodium 22β-hydroxyoleanonate (see below) removed by filtration. Steam-distillation of the acidified (dilute sulphuric acid) filtrate gave 0·675 milliequiv. of steam-volatile acid. Evaporation of the titrated distillate *in vacuo* furnished the sodium salt of the acid. This sodium salt (48 mg.) was converted into the *p*-bromophenacyl ester. Recrystallised from hexane this had m. p. 100·5—101°, undepressed on admixture with an authentic specimen (m. p. 100—100·5°; Smith and Rosenbaum, *J. Amer. Chem. Soc.*, 1951, **73**, 3843). The *p*-phenylphenacyl ester, prepared similarly and crystallised from methanol, had m. p. 142—143°, undepressed on admixture with an authentic specimen (Smith and Rosenbaum, *loc. cit.*) of the same m. p.

The sodium salt removed by filtration (see below) was acidified and the product crystallised from aqueous methanol, to give 22β-hydroxyoleanonic acid, m. p. 233—236° (decomp.), $[\alpha]_D$ +90° (*c*, 1·55), undepressed in m. p. on admixture with an authentic specimen of m. p. 230—

234° (decomp.), $[\alpha]_D$ +92° (Barton and de Mayo, *loc. cit.*, p. 900). Methylation with diazomethane furnished methyl 22β-hydroxyoleanonate, m. p. (from methanol after drying *in vacuo* at 95°) 188—189°, $[\alpha]_D$ +86° (*c*, 2·06), undepressed in m. p. on admixture with an authentic specimen (Barton and de Mayo, *loc. cit.*, p. 900). Oxidation of this ester (79 mg.) in "AnalaR" acetic acid (3 ml.) with chromium trioxide (18 mg.) in 2 drops of water overnight at room temperature gave methyl 22-oxo-oleanonate, m. p. (from methanol) 204—206°, $[\alpha]_D$ +40° (*c*, 2·38), undepressed in m. p. on admixture with an authentic specimen (Barton and de Mayo, *loc. cit.*, p. 900).

Methyl 22β-Benzoyloxyoleanolate Benzoate.—A solution of 22β-hydroxyoleanonic acid (52 mg.) in "AnalaR" acetic acid (6 ml.) was hydrogenated overnight with a platinum catalyst. The product was methylated with diazomethane and then refluxed with methanolic potassium hydroxide (5%; 5 ml.) for 15 min. The resulting methyl 22β-hydroxyoleanolate in dry pyridine (1 ml.) was treated with redistilled benzoyl chloride (62 mg.) and left at room temperature for 4 days. Chromatography over alumina and elution with benzene gave *methyl 22β-benzoyloxyoleanolate benzoate* (37 mg.), m. p. (from chloroform–methanol) 210·5—212°, $[\alpha]_D$ +60° (*c*, 1·87), $\lambda_{max.}$ 229 mμ (ε 29,700) (Found: C, 78·0; H, 8·35. $C_{45}H_{58}O_6$ requires C, 77·75; H, 8·4%).

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Properties of Periodate-oxidised Polysaccharides. Part III. Estimation of α-Glycol Groupings in a Polysaccharide.*

By VINCENT C. BARRY, JOAN E. MCCORMICK, and P. W. D. MITCHELL.

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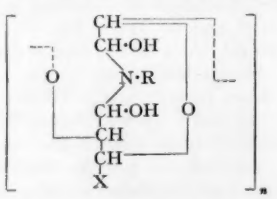
The nitrogen and sulphur contents of the polymers obtained by the condensation of periodate-oxidised polysaccharides with *iso*nicotinhydrazide and thiosemicarbazide give a measure of the proportion of sugar units vulnerable to periodate oxidation in the polysaccharides.

IN Parts I and II,* a description was given of some new derivatives of oxystarch (periodate-oxidised starch) obtained by condensation with carbonyl reagents, *e.g.*, thiosemicarbazide, hydrazine, *iso*nicotinhydrazide (isoniazid), and with various aromatic bases, *e.g.*, *p*-aminobenzoic acid. Analysis of the polymers obtained from oxystarch and thiosemicarbazide or isoniazid showed that one molecule of reagent had condensed with each potential dialdehyde group and accordingly a cyclic structure was proposed for these condensation products. Products of a similar kind have been obtained by condensation of periodate-oxidised trehalose and raffinose with *p*-nitrophenylhydrazine (Akiya, Okui, and Suzuki,



R = NH·CO–C₆H₄–N or NH·CS·NH₂.

X = CH_2·OH (amylose, amylopectin, waxy maize starch), or CO_2H (alginic acid).

J. Pharm. Soc. Japan, 1952, **72**, 891; *Chem. Abs.*, 1953, **47**, 7447); these also contained only one condensed molecule of reagent for each oxidised α-glycol group. The present paper is concerned with the estimation of the proportion of α-glycol groups in various

* Parts I & II, Barry and Mitchell, *J.*, 1953, 3610, 3631.

polysaccharides from the composition of the thiosemicarbazide and isoniazid condensation products prepared from the periodate-oxidised polysaccharides, and the comparison of these values with those obtained by previously known methods.

It is now well established that amylose, amylopectin, and waxy maize starch are glucose polymers in which the hexose units are almost all joined by α-1 : 4-linkages and that the mannuronic acid units in alginic acid are β-1 : 4-linked (Hirst, Jones, and Jones, *J.*, 1939, 1880). In these polysaccharides, therefore, after oxidation with periodate, each hexose or hexuronic acid unit will provide a reactive centre for the condensation of one molecule of

TABLE 1.

	Thiosemicarbazide polymer				Isoniazid polymer	
	Reqd. (%)		Found (%)		Reqd. (%)	Found (%)
Polysaccharide	N	S	N	S	N	N
Amylose	16·7	12·7	16·1	12·1	14·1	13·9
Amylopectin	16·7	12·7	15·9	11·8	14·1	14·1
Waxy maize starch	16·7	12·7	15·2	11·8	14·1	14·4
Alginic acid	15·8	12·1	17·5	13·0	13·5	13·1

carbonyl reagent. Gravimetric analyses of the condensates will then permit the calculation of the proportion of α-glycol groups in the original polysaccharide. Table 1 shows the nitrogen and sulphur contents of the thiosemicarbazide and isoniazid polymers derived from the oxypolysaccharides, together with the values required by the theory assuming that all the linkages present in the molecules are 1 : 4. The deviations are small, particularly for the isoniazid polymers, and confirm the large preponderance in these polysaccharides of 1 : 4-linkages. It was of particular interest, therefore, to apply this method to some polysaccharides which are claimed to contain 1 : 3-linkages, *e.g.*, xylan from *Rhodymenia palmata*, nigeran from *Aspergillus niger*, Floridean starch and laminarin, and Table 2 gives the appropriate results. In the last part of the Table the α-glycol contents calculated from the analytical figures are compared with those derived from the periodate consumption.

TABLE 2.

	Thiosemicarbazide polymers				Isoniazid polymers		α-Glycol content (%)		
	Required for 100% α-glycol		Found		Required for 100% α-glycol	Found	From periodate	From thiosemicarbazide polymer [a]	From isoniazid polymer
Polysaccharide	N	S	N	S	N	N			
Xylan	19·0	14·5	14·5	11·9	15·7	13·2	69	72, 73	72
Nigeran	16·7	12·7	10·6	8·3	14·1	10·3	48 [b]	53, 55	60
Laminarin	—	—	—	—	14·1	1·5	—	—	6·1
Floridean starch	16·7	12·7	16·4	12·7	14·1	14·1	97	97, 100	100

[a] The first figure is based on the nitrogen analysis and the second on the sulphur. [b] Value obtained by Barker, Bourne, and Stacey, *J.*, 1953, 3084.

Methylation studies previously conducted with the xylan have indicated the presence of 1 : 4- and 1 : 3-linkages in this polysaccharide, and periodate consumption indicated that about 80% of the linkages are 1 : 4 [(*a*) Percival and Chanda, (*b*) Barry, Dillon, Hawkins, and O'Colla, *Nature*, 1950, **166**, 787]. The figures for this xylan (Table 2) lend support to the findings of these authors. Also, an important conclusion may be arrived at as to the homogeneity of the xylan. If it were a mixture of two polysaccharides built from 1 : 3- and 1 : 4-linked xylose anhydride residues respectively, then the polymer separating after condensation of the oxidised material with isoniazid or with thiosemicarbazide would be derived solely from the 1 : 4-linked polyoses and would thus contain a higher nitrogen content.

The polyglucose, nigeran, has been shown in methylation studies by Barker, Bourne, and Stacey (*loc. cit.*) to contain approximately equal proportions of 1 : 3- and 1 : 4-linked units. As seen in Table 2, the analyses of the derivatives prepared confirm these findings and also the conclusion of these authors that the two types of linkage are present in the one polysaccharide molecule.

The result obtained with laminarin is interesting. If one assumes that condensation of the carbonyl reagent takes place only at the non-reducing end of the periodate-oxidised polysaccharide, then the chain-length calculated from the nitrogen content works out at approximately 16 glucose units This is the degree of polymerisation found in this polysaccharide by Barry's method (*J.*, 1942, 578) and is of the same order as that found by Percival and his co-workers from methylation studies (Connell, Hirst, and Percival, *J.*, 1950, 3494 ; Percival and Ross, *J.*, 1951, 720).

Examined in this way Floridean starch has given results which do not agree in some respects with previous reports. Barry, Halsall, Hirst, and Jones (*J.*, 1949, 1468) suggested from the periodate consumption and from the fact that glucose could be identified, by paper chromatography, among the hydrolysis products of the oxidised starch, that their polysaccharide contained a proportion of 1 : 3-linked glucose residues. More recently, O'Colla (*Proc. Roy. Irish Acad.*, 1953, **55**, *B*, 321) reported failure to find conclusive evidence of the presence of 1 : 3-linkages; however, as his material contained about 20% of a galactan which he was unable to remove, it must be admitted that there remained a considerable uncertainty as to the broad structural characteristics of this polysaccharide. The sample of Floridean starch described in the present report was isolated as previously described (Barry *et al.*, 1949, *loc. cit.*) from *Dilsea edulis* collected on the Kerry coast in August 1953. It was purified by repeated precipitation with alcohol followed by dialysis. On hydrolysis this sample yielded only glucose. As Table 2 shows, there is no evidence that this polysaccharide contains 1 : 3-linkages any more than does amylose. Further, when the periodate-oxidised polysaccharide was hydrolysed by acid, paper chromatography of the hydrolysis products failed to show the presence of glucose. The oxidised xylan and nigeran on the other hand, when similarly treated, were shown to contain xylose and glucose respectively.

It might be argued that the failure to detect 1 : 3-linkages in Floridean starch was due to over-oxidation. The composition of the thiosemicarbazide and isoniazid derivatives however, shows that this was unlikely since it gives a measure of the α-glycol content of the portion of the polysaccharide molecule remaining after oxidation. The α-glycol content deduced from analysis of these derivatives could only be too high if the units removed by over-oxidation were 1 : 3-linked. Hexose units removed in this way are generally believed to come from the reducing end of the molecule (Halsall, Hirst, and Jones, *J.*, 1947, 1429; Neumuller and Vasseur, *Arkiv Kemi, Min., Geol.*, 1953, **5**, 235; Head, *J. Text. Inst.*, 1953, **44**, T209), and a chain of 1 : 3-linked units at such a position in a polysaccharide seems improbable. In any event removal of each hexose molecule, whether 1 : 3- or 1 : 4-linked, consumes according to Neumuller and Vasseur six mols. of periodate as compared with the consumption of one mol. in normal oxidation, and, if over-oxidation of the Floridean starch had taken place to any considerable degree, the overall consumption of periodate would have been greater than the 1 mol. per glucose mol. actually obtained for our Floridean starch. It seems justifiable, therefore, to conclude that this material contained no significant proportion of 1 : 3-linked glucose units.

Experimental

All polysaccharide materials were dried at 100°/10 mm.

Thiosemicarbazide and Isoniazid Derivatives of Oxidised Amylose, Amylopectin, and Waxy Maize Starch.—The polysaccharide (2 g.) was kept for 48 hr. with sodium metaperiodate solution (144 c.c.; 12·547 g. per l.). The oxidised material was filtered, washed free from inorganic material, and dissolved in water (100 c.c.) on a boiling-water bath during 1 hr. The concentration of the solution in each case was determined by evaporation to dryness of an aliquot. The solutions had $[\alpha]_D^{24}$ (in H_2O) as follows: oxyamylose, +24·3° (*c* 1·088); oxyamylopectin, +20·5° (*c* 1·666); waxy maize oxystarch, +20·5° (*c* 1·999). Two portions (25 c.c. each) of the oxystarch solution were mixed with isoniazid (0·85 g.) in water (50 c.c.) and thiosemicarbazide (0·56 g.) in water (50 c.c.) respectively. An immediate precipitate was formed in each case. These were separated in the centrifuge and washed with water, alcohol, and finally ether. The yields for the isoniazid and thiosemicarbazide products were, respectively: from oxyamylose, 99, 88; oxyamylopectin, 99, 90; waxy maize starch, 100, 91%.

Thiosemicarbazide and Isoniazid Derivatives of Oxidised Alginic Acid.—Sodium alginate (Manucol) (2 g.) was treated with sodium metaperiodate solution (214 c.c.; 12·547 g. per l.). The alginate dissolved slowly and after 48 hr. ethylene glycol (5 c.c.) was added and the solution dialysed against running water for 11 days. After filtering through Celite, the filtrate had $[\alpha]_D^{18}$ +135° (*c* 0·516 in H_2O). Two 50-c.c. portions were used as described earlier for the preparation of the thiosemicarbazide and isoniazid polymers. In this case the condensation products remained in solution and were precipitated when the solutions were made slightly acid. The products were isolated and dried as above The yield of isoniazid derivative was 76% and of the thiosemicarbazide derivative 44%.

Xylan Derivatives.—The xylan was isolated from the red alga, *Rhodymenia palmata*, by Barry and Dillon's method (*Nature*, 1940, **146**, 620) and had $[\alpha]_D^{23}$ −97·1° (*c* 0·3912 in H_2O). The pentosan (2 g.) was treated in water (50 c.c.) with sodium metaperiodate (3·57 g.; 10% excess) in water (100 c.c.). Ethylene glycol (2 c.c.) was added after 72 hr. The solution, dialysed against running water for 11 days, had $[\alpha]_D^{23}$ +85° (*c* 0·88 in H_2O). The isoniazid and thiosemicarbazide condensation products were prepared in good yield as above. It was necessary to add a little sodium chloride to effect separation.

The periodate consumption and yield of formic acid were measured in a separate experiment by the method of Halsall, Hirst, and Jones (*J.*, 1947, 1430). Xylan (0·7 g.), in water, was added to sodium metaperiodate (20 c.c.; 0·2525M) and the volume brought to 200 c.c. The course of the oxidation is tabulated.

Time (hr.)	3	6	23	27	47	52	71	119
Consumption of periodate (mol. per xylose residue)	0·304	0·427	0·592	0·595	0·630	0·640	0·671	0·686
Average chain-length, calc. from formic acid produced	18·2	18·2	15·7	15·8	15·8	15·7	15·7	—

The figures in the last row represent the number of xylose units for each non-reducing end-group. Complete reliance cannot be placed on this method of end-group assay because of the difficulty of determining the end-point in the formic acid titration. (For a critical evaluation of the method, see Morrison, Knyper, and Orton, *J. Amer. Chem. Soc.*, 1953, **75**, 1502.)

Hydrolysis of Oxyxylan.—(a) *Identification of xylose.* The above oxyxylan solution (100 c.c.) was dialysed against running water for 24 hr. and then heated on the water-bath (6 hr.) with an equal volume of 6N-sulphuric acid. It was neutralised ($BaCO_3$), filtered, and concentrated under reduced pressure to a small volume. A paper chromatogram run in *n*-butanol–pyridine–water–benzene (5 : 3 : 3 : 1) gave one spot, R_g (g = glucose) 1·42. Similar treatment of the unoxidised xylan gave a spot having R_g 1·44.

(b) *Isolation of xylosazone.* Xylan (2 g.) in water (25 c.c.) was kept with sodium metaperiodate (60 c.c.; 0·25M) for 90 hr., then treated with a few c.c. of 10% aqueous ammonia (cf. Barry, Dillon, Hawkins, and O'Colla, *loc. cit.*) and neutralised with 10% acetic acid, giving a white gelatinous precipitate. This was separated, washed, and dried, as usual, to a white powder (0·5 g.) which was hydrolysed on the water-bath (1·6 hr.) with 0·5N-sulphuric acid (20 c.c.). The solution was then neutralised ($BaCO_3$), filtered, and concentrated under reduced pressure. Treatment of this at room temperature with phenylhydrazine (1 c.c.) in 33% acetic acid (3 c.c.) gave a gummy precipitate which on recrystallisation from benzene yielded glyoxalosazone, m. p. 166—167°. The filtrate after removal of the gum was warmed on the water-bath for 15 min., then kept for 1½ hr. Characteristic D-xylosazone (44 mg.) separated. This had *M* (determined spectrophotometrically) 329·4 (Required, 328) (this method will be described in a subsequent paper).

Hydrolysis of the Oxyxylan–Isoniazid Polymer.—The polymer (0·6 g.) was warmed on the water-bath (1½ hr.) with 0·5N-sulphuric acid (24 c.c.). After neutralisation and the usual treatment, D-xylosazone was obtained, identity being confirmed by paper chromatography (Rutter, *Nature*, 1948, **161**, 435; *Analyst*, 1950, **75**, 37) with benzene–alcohol (9 : 1).

Derivatives of Nigeran.—Nigeran (0·178 g.) was kept with a solution of sodium metaperiodate (0·282 g. in 35 c.c.) for 72 hr. Lead acetate (in slight excess) was added and the precipitate removed by filtration. Rotational measurements before and after addition of the lead acetate showed that more than half of the material had been lost. The precipitate was washed with water, and the combined washings and filtrate were treated with sufficient sulphuric acid (10%) to remove excess of lead. The filtrate, in two parts, was treated as above for the preparation of the isoniazid and thiosemicarbazide derivatives. The precipitates were formed slowly and after 24 hr. were separated on the centrifuge, washed, and dried (about 15 mg. in each case).

Derivatives of Floridean Starch.—Floridean starch (2 g.) was treated with sodium metaperiodate solution (144 c.c.; 0·0585M). After 48 hr., ethylene glycol (5 c.c.) was added and the

solution dialysed for 12 days against running water. Flocculent material was dissolved by warming and the solution filtered through Celite. Two 50-c.c. portions of the solution ($[\alpha]_D^{20}$ +15·7°; *c* 0·838 in H_2O) were treated with isoniazid (0·828 g. in water, 50 c.c.) and thiosemicarbazide (0·56 g. in water, 50 c.c.), severally. Precipitates were formed slowly and after 24 hr. were separated on the centrifuge, washed, and dried as usual. The yield of isoniazid product was 0·716 g. (100%) and of the thiosemicarbazide product 0·571 g. (97%).

Periodate Consumption of Floridean Starch.—(a) *With sodium metaperiodate.* The starch (0·693 g.) dissolved in water was mixed with the periodate solution (20 c.c.; 0·2386M) and diluted to 150 c.c. The periodate consumption (mol. per anhydroglucose unit) was: 0·71 (2·5 hr.), 0·90 (22·0 hr.), 0·92 (26·5 hr.), 0·93 (29·5 hr.), 0·97 (50·5 hr.), 0·97 (69·7 hr.), 0·97 (143·0 hr.).

(b) *With potassium metaperiodate.* The starch (0·7 g.) was dissolved in water containing potassium chloride (7·0 g.), sodium metaperiodate (20 c.c.; 0·244M) was added, and the solution was shaken for 8 days. Estimation of the periodate present showed that 1 mol. of anhydroglucose had consumed 0·96 mol. of periodate.

Hydrolysis of Floridean Oxystarch.—The solution (108 c.c.) resulting from the previous estimation was filtered to remove potassium periodate. It was then treated with lead acetate solution and, after removal of the precipitate, excess of lead was precipitated with sulphuric acid (10%). The filtrate was concentrated to 7 c.c. under reduced pressure, mixed with an equal volume of N-sulphuric acid and warmed on the water-bath for 8 hr. After neutralisation with barium carbonate, the filtrate was concentrated under reduced pressure. A drop of this concentrated solution was run on a paper chromatogram with *n*-butanol–pyridine–benzene–water (5 : 3 : 3 : 1), and the paper developed with aniline phthalate. There was no evidence of the presence of glucose.

The remaining portion of the hydrolysate on treatment at room temperature as described above with phenylhydrazine and acetic acid gave a crystalline precipitate which proved to be mainly glyoxalosazone. After removal of the latter, the filtrate was heated on the water-bath (1 hr.). No glucosazone separated nor was any evidence of it obtained on a paper chromatogram (Rutter, *loc. cit.*).

Laminarin–Isoniazid Derivative.—An aqueous solution of laminarin was treated with excess of sodium metaperiodate solution and kept for 72 hr. The polysaccharide which had separated from solution was removed by filtration, washed with water, and dried. It was then redissolved in hot water, and an excess of an aqueous solution of isoniazid added. After a week, the off-white granular deposit was separated, washed with water, ethanol, and ether, and dried.

Two of us (P. W. D. M. and J. E. McC.) are Lasdon Foundation Fellows of University College, Dublin. We are grateful to Professor M. Stacey, F.R.S., for the sample of nigeran.

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Nuclear Magnetic Resonance Spectra and the Structure of Infusible White Precipitate.

By C. M. Deeley and R. E. Richards.

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Proton magnetic resonance spectra are given for samples of infusible white precipitate prepared by three different methods, and for a sample of fusible white precipitate. The results support the structure $NH_2{\cdot}HgCl$ for infusible white precipitate and exclude the structures NHg_2Cl,NH_4Cl and $x HgO,(1-x)HgCl_2,2NH_3$. It is suggested that preparations of infusible white precipitate may often contain impurities of mercuric chloride, of fusible white precipitate, or of $x HgO,(1-x)HgCl_2,2NH_3$, according to the conditions.

Gmelin–Kraut's "Handbuch der anorganischen Chemie" lists the formulæ of some twenty compounds which have been thought to be formed by the interaction of mercuric chloride and ammonia solutions. The structure of one of these, namely "infusible white precipitate," has been investigated by many workers during the past century. It has been formulated by Rammelsberg (*J. pr. Chem.*, 1888, **38**, 558) as NHg_2Cl,NH_4Cl (I), by Franklin (*J. Amer. Chem. Soc.*, 1907, **29**, 35) as $NH_2{\cdot}HgCl$ (II), and by Britton and Wilson (*J.*, 1933, 601, 1045) as $x HgO,(1-x)HgCl_2,2NH_3$ (III). Quantitative chemical analysis has not provided unambiguous evidence in favour of any one of these structures.

Samples of infusible white precipitate have been prepared by various methods, and their proton magnetic resonance spectra observed. The shapes and mean-square widths of these spectra depend upon the grouping and internuclear separation of the hydrogen atoms (see, *e.g.*, Purcell, *Science*, 1948, **107**, 433; Pake, *Amer. J. Physics*, 1950, **18**, 438, 473; Richards and Smith, *Trans. Faraday Soc.*, 1951, **47**, 1261; Smith, *Quart. Reviews*, 1953, **7**, 279), and thereby provide a method of distinguishing between structures (I), (II), and (III).

Rammelsberg's formula (I) was put forward as part of a scheme which formulated many of the mercuric chloride–ammonia compounds as double salts of ammonium chloride. Franklin's formula (II) was supported by Hofmann and Marburg (*Annalen*, 1899, **305**, 191) on the basis of experiments in which the actions of silver nitrate and of calcium hydroxide on the precipitate were investigated quantitatively.

In 1933 Britton and Wilson (*loc. cit.*) suggested formula (III) on the basis of conductometric and electrometric titrations of mercuric chloride and aqueous ammonia. This formula has recently received further support from Glasson and Gregg (*J.*, 1953, 1493) who measured the rate of thermal decomposition and the dissociation pressure of infusible white precipitate, and compared the activation energy of the reaction with those of the decomposition of compounds of known formulæ. They also measured the loss in weight due to the elimination of ammonia and found the results to be consistent with formula (III).

Lipscomb (*Acta Cryst.*, 1951, **4**, 266) interpreted *X*-ray diffraction patterns of infusible white precipitate in terms of long chains of alternate mercury atoms and $-NH_2^+-$groups, with the chloride ions packed between the chains. An analogous structure has also been found for the corresponding bromide (*idem, ibid.*, 1952, **5**, 604).

The diversity of these conclusions may be due partly to the different methods of preparation used. Thus, whereas Franklin used the action of liquid ammonia or of sodamide on solid mercuric chloride, Lipscomb used 0·685N-ammonia solution and mercurous chloride, Britton and Wilson used 0·1027N-ammonia solution and 0·025M-mercuric chloride solution, and Glasson and Gregg used the methods of the British Pharmacopœia (1914).

Experimental

(a) *Preparation of Samples.—Infusible white precipitate, sample A.* A solution of **60** g. of "AnalaR" mercuric chloride in 1200 c.c. of water was run slowly into 480 c.c. of N-ammonia

solution, with stirring. The precipitate was washed with a small quantity of water and dried at 30°. Analysis of the mercury content by precipitation as $Cu(en)_2HgI_4$ (Vogel, "Quantitative Analysis," Longmans, London, 1943, p. 505), where en represents ethylenediamine, the chlorine as silver chloride, and the nitrogen by Kjeldahl's method gave Hg, 78·7; Cl, 16·7; NH_3, 4·93% (Calc. for $HgNH_2Cl$: Hg, 79·6; Cl, 14·1; NH_3, 6·8%. Calc. for $0{\cdot}25HgCl_2,0{\cdot}75HgNH_2Cl$: Hg, 78·0; Cl, 17·2; NH_3, 5·0%). If left in contact with water, the precipitate becomes yellow, probably owing to the formation of Hg_2ONH_2Cl (Brauer, "Handbuch der Preparativen anorganischen Chemie," Ferdinand Enke Verlag, 1951, Vol. 6, p. 824).

Infusible white precipitate, sample B. This was prepared as for sample A, but with use of 3N-ammonia solution (Found: Hg, 77·4; Cl, 13·8; NH_3, 7·0%).

Infusible white precipitate, sample C. A small amount of sample A was dissolved in "AnalaR" ammonia solution (*d* 0·88) (Saha and Chouhudri, *Z. anorg. Chem.*, 1910, **67**, 357) and then allowed to crystallise slowly in a vacuum-desiccator over concentrated sulphuric acid. The yield was very small, but the product was crystalline.

Fusible white precipitate, $HgCl_2,2NH_3$. Alexander's method (Reaktionen von Salzen in Aethyl Acetat, Diss., Giessen, 1899, 9) as used by Palmer ("Experimental Inorganic Chemistry," C.U.P., 1953) was adopted, in which a stream of dry ammonia was passed into a solution of mercuric chloride in anhydrous ethyl acetate.

The analyses quoted above are probably not very reliable as the results appear to vary with the method used (Lipscomb, *Analyt. Chem.*, 1953, **25**, 737). The mercury and chlorine analyses were internally consistent but it was difficult to get reproducible results for the ammonia estimation. Similar difficulties have been reported by Brodersen and Rüdorff (*Z. anorg. Chem.*, 1954, **275**, 141).

(b) *Nuclear Resonance Measurements.*—The apparatus used has already been described (Richards and Smith, *loc. cit.*; Pratt and Richards, *Trans. Faraday Soc.*, 1953, **49**, 744). The radio-frequency coil is made of bare silver wire wound internally in a fired soapstone former. The sealed glass tube containing the sample fits snugly into the coil. Measurements on an empty sample tube have shown that the coil and former give no proton resonance signal.

The nuclear resonance spectrometer produces a record of the first differential of the absorption line, and the absorption line itself is obtained by numerical or graphical integration of the experimental record. The broadening or width of the adsorption line is expressed in terms of the mean-square width, or second moment in gauss^2. The second moment (ΔH_2^2) is given by

$$\int_{-\infty}^{+\infty} f(H) \cdot H^2 dH \Big/ \int_{-\infty}^{+\infty} f(H) \cdot dH$$

where $f(H)$ is the line shape function, and H is the distance in gauss from the centre of the line. Line widths can readily be expressed in frequency units instead of magnetic field units by means of the relation $h\nu = \mu H/I$, where h is Planck's constant, ν is the frequency, μ is the nuclear magnetic moment, I the nuclear spin quantum number, and H the magnetic field strength.

The samples were all studied at 90° K in liquid oxygen, and sample A and the fusible white precipitate were also measured in liquid hydrogen at 20° K.

Results.—The proton resonance spectra at 90° K are shown in Figs. 1—4, which show for each sample a typical experimental derivative curve and the integrated absorption curve. The double-ended arrows represent the magnetic field modulation used. The spectrum of sample A at 20° K was identical with that at 90° K, but the spectrum of fusible white precipitate at 20° K was broader than at 90° K and resembled an incompletely broadened line due to an equilateral triangular group of protons. The points superimposed on the absorption curves are calculated ones which will be referred to in the discussion.

The second moments of the curves obtained at 90° K, and the line widths (expressed as the separation of the outer maxima of the derivative curves) are given in the Table below together with their standard deviations.

	Second moment, gauss^2	Line width, gauss	Number of runs taken
Sample A	18·3 ± 1·0	10·7 ± 0·3	11
B	18·6 ± 1·1	11·4 ± 0·2	8
C	20·25 ± 1·5	11·7 ± 0·6	6
Fusible white precipitate	10·2 ± 0·7	3·85 ± 0·15	4

The signal obtained from sample C was weak, since only a small amount was available and so the second moment obtained may be less reliable than in the other cases.

FIG. 1. *Infusible white precipitate, sample A.—Derivative and absorption curves at* 90° K. *Dots represent points calculated for pairs of protons,* 1·688 Å *apart* ($\alpha = 3\mu/2r^3 = 4{\cdot}4$ *gauss*) *with a broadening function* $\beta^2 = 3{\cdot}6$ *gauss*^{2}.

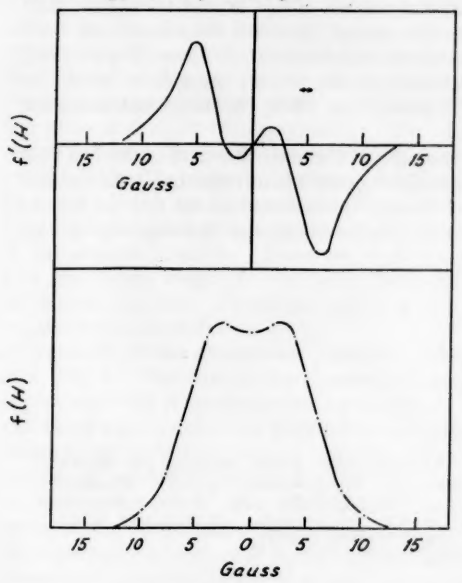


FIG. 2. *Infusible white precipitate, sample B.—Derivative and absorption curves at* 90° K. *Dots are calculated for a mixture of* $NH_2{\cdot}HgCl$ *and* $HgCl_2{,}2NH_3$ *in ratio* 0·84 : 0·16.

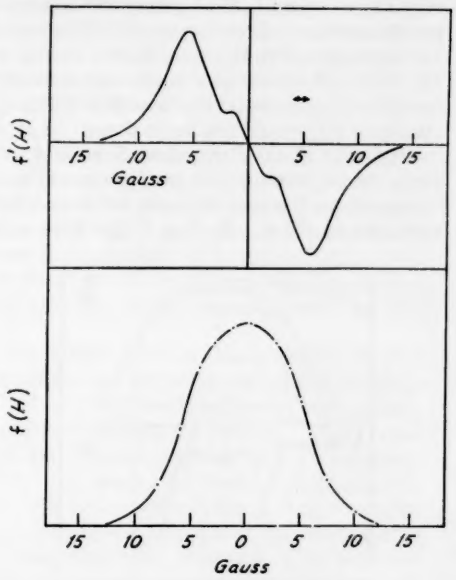


FIG. 3. *Infusible white precipitate, sample C.—Derivative and absorption curves at* 90° K. *Dots represent points calculated for pairs of protons* 1·688 Å *apart* ($\alpha = 3\mu/2r^3 = 4{\cdot}4$ *gauss*) *with a broadening function* $\beta^2 = 3{\cdot}6$ *gauss*^{2}.

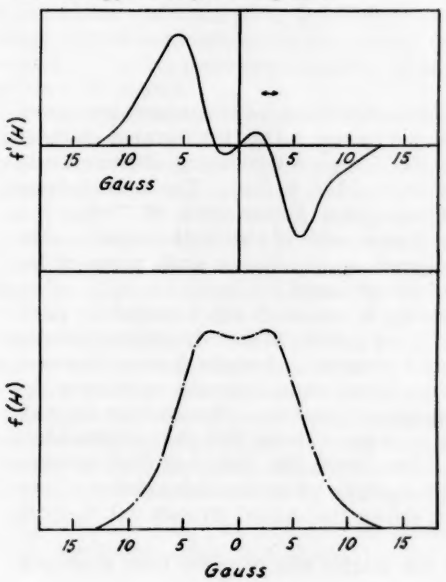
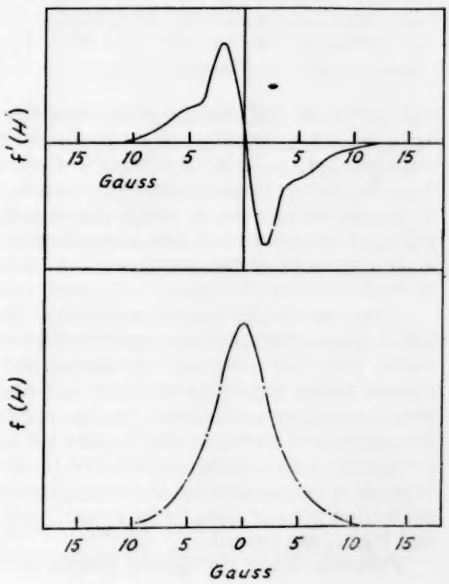


FIG. 4. *Fusible white precipitate.—Derivative and absorption curves at* 90° K. *Dots are calculated for equilateral triangle of protons* 1·682 Å *apart rotating about an axis perpendicular to their plane,* $\alpha = 4{\cdot}442$ *gauss and* $\beta^2 = 3{\cdot}5$ *gauss*^{2}.



Discussion

In structure (I; NHg_2Cl,NH_4Cl) the hydrogen atoms are arranged in tetrahedral groups, in (II; $NH_2{\cdot}HgCl$) they are grouped in pairs, and in [III; xHgO,$(1-x)HgCl_2,2NH_3$] they are arranged at the corners of equilateral triangles. The proton resonance line shapes and their approximate second moments for these three rigid arrangements of protons are shown in Fig. 5 (Andrew and Bersohn, *J. Chem. Phys.*, 1950, **18**, 159). If appreciable molecular motion occurred in the solids, these lines would be considerably narrowed (Gutowsky and Pake, *J. Chem. Phys.*, 1950, **18**, 162), but the one for structure (II) would retain its shape.

Infusible White Precipitate, Sample A.—The shape of the experimental curve fits that expected for formula (II), and its second moment (18·3 gauss^2) is as expected. As the line remained unchanged between 20° K and 90° K it may be assumed to be due to a rigid structure at 90° K. In Fig. 1 the dots represent points calculated theoretically (Pake,

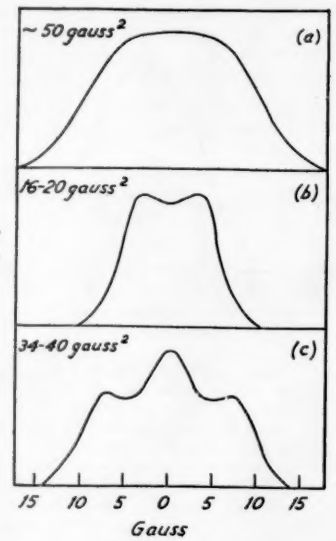


Fig. 5. *Absorption curves expected for different structures.*—(a) *Tetrahedral groups.* Rammelsberg, NHg_2Cl,NH_4Cl. (b) *Pairs.* Franklin, $NH_2{\cdot}HgCl$. (c) *Triangles.* Britton and Wilson, $xH_2O,(1-x)HgCl_2,2NH_3$.

ibid., 1948, **16**, 327) for the absorption line of pairs of protons, 1·688 Å apart, broadened by a Gaussian function of mean-square width 3·6 gauss^2. This inter-proton distance corresponds to an N–H distance of 1·03 Å, if the HNH angle is tetrahedral, as seems likely from the *X*-ray measurements (Lipscomb, *Acta Cryst.*, 1951, **4**, 266). The N–H distance in the ammonium ion is 1·03 Å (Levy and Peterson, *Phys. Review*, 1952, **86**, 766). The width of the absorption line depends upon the inverse cube of the H–H distance. The second moment of the calculated line, which depends on the inverse sixth power of the H–H distance, is 19·1 gauss^2 compared with 18·3 gauss^2 found.

These results show conclusively that the protons in sample A are arranged in pairs, and this gives very strong support to structure (II). Fig. 5 shows that the other structures would give very different line shapes and second moments. Sample A may, however, contain other impurities which do not contain hydrogen atoms, because such impurities would make no contribution to the proton resonance spectrum. The analysis suggests the presence of mercuric chloride which is probably co-precipitated with the infusible white precipitate. Broderson and Rüdorff (*Z. anorg. Chem.*, 1954, **275**, 141) find that mercuric bromide is co-precipitated in the preparation of $NH_2{\cdot}HgBr$ when ammonia solution of concentration greater than 0·09N is used, and have shown that mixed crystals of $NH_2{\cdot}HgBr$ and $HgBr_2$ are formed.

Infusible White Precipitate, Sample B.—As this sample was prepared from more con-

centrated ammonia solution than A, it is possible that the formation of mercuric chloride diammine is facilitated. The analysis of this sample is consistent with this view. If this is correct, its proton resonance spectrum would be expected to be a superposition of that of infusible white precipitate and of fusible white precipitate in the appropriate proportions. The absorption line of fusible white precipitate at 90° K, obtained experimentally, is shown in Fig. 4 and discussed below. The dots in Fig. 2 represent points obtained by superposing the experimental absorption curves of sample A (Fig. 1) (which is due only to the infusible white precipitate, any mercuric chloride impurity making no contribution to the signal) and of fusible white precipitate (Fig. 4), in such a way that their areas are in the ratio of 0·84 : 0·16 respectively. The close fit of these points with the experimental curve in Fig. 2 supports the view that when concentrated ammonia solution is used to prepare infusible white precipitate some fusible white precipitate ($HgCl_2,2NH_3$) may also be formed. For the corresponding bromides, Broderson and Rüdorff (*loc. cit.*) report that they have obtained mixed crystals of NH_2·HgBr and $HgBr_2,2NH_3$ in the presence of traces of ammonium bromide. However, it is not possible to distinguish between $HgCl_2,2NH_3$ and the basic xHgO,$(1-x)HgCl_2,2NH_3$ since they would give very similar nuclear resonance signals. Therefore xHgO,$(1-x)HgCl_2,2NH_3$ could equally well be the impurity in sample B.

Infusible White Precipitate, Sample C.—The absorption curve is closely similar to that of A, Fig. 1. The dots on the absorption curve in Fig. 3 are the points calculated for pairs of protons 1·688 Å apart as done for sample A. It shows the central minimum very clearly, and there can therefore be very little hydrogen-containing impurity present. Quite small amounts of proton-containing impurity in which the protons occur in any arrangement except in relatively isolated pairs, are sufficient to mask the central minimum in the absorption curve. For example, if enamelled wire coils are used, the proton resonance signal of the very small amount of enamel present is sufficient to prevent the minimum in the absorption spectrum of infusible white precipitate from being observed. The presence of mercuric chloride impurity would have no effect on the proton resonance spectrum but, in view of the well-formed crystals of sample C obtained, and of the fact that the compound was recrystallised from concentrated ammonia solution, it is unlikely that much mercuric chloride can be present.

Fusible White Precipitate.—*X*-Ray measurements (Lipscomb, *Analyt. Chem.*, 1953, **25**, 737; MacGillavry and Bijvoet, *Z. Krist.*, 1936, **94**, 231) have been interpreted in terms of a cubic lattice of linear $(NH_3–Hg–NH_3)^{++}$ ions and chloride ions, the mercury ammine ions being aligned randomly along the crystal axes. A rigid structure of this type would be expected to give a proton resonance spectrum of the shape of Fig. 5*c*, and a second moment of about 36 gauss^2.

The experimental curve at 90° K shows only a single maximum and has a second moment of $10·2 \pm 0·7$ gauss^2. If the NH_3 groups were undergoing rotational reorientation about the Hg–N axis frequently enough, a line very similar to the experimental one would be expected, and its second moment would be about $\frac{1}{4}$ of 36 gauss^2, *i.e.*, ~9 gauss^2. The circles in Fig. 4 represent the points calculated (Andrew and Bersohn, *J. Chem. Phys.*, 1950, **18**, 159) theoretically for an equilateral triangle of protons 1·682 Å apart, rotating about an axis perpendicular to their plane, and broadened by a gaussian function of second moment 3·5 gauss^2.

The proton resonance spectrum at 20° K is still partially narrowed, and its shape and width suggest that 20° K is within the range of the line-width transition from the narrowed line to the spectrum characteristic of the " rigid " structure.

This freedom of motion probably occurs because the NH_3 groups are in a very open lattice and spaced well away from the chloride ions. Similar effects have been observed with dimethylmercury (Gutowsky and Pake, *J. Chem. Phys.*, 1950, **18**, 162). The greater rigidity of the NH_2 groups in infusible white precipitate is probably associated with the long chains present in which the nitrogen atoms are linked each to two mercury atoms (–Hg–$\overset{+}{N}H_2$–Hg–$\overset{+}{N}H_2$–, etc.) (Lispcomb, *Analyt. Chem.*, 1953, **25**, 737).

In conclusion, it has been shown that the proton resonance spectrum of infusible white

precipitate is consistent with the structure NH_2·HgCl. The structures NHg_2Cl,NH_4Cl and $xHgO,(1-x)HgCl_2,2NH_3$ are excluded by the proton resonance spectra, at least for the samples studied. It seems likely that preparations of infusible white precipitate are often contaminated with mercuric chloride or with fusible white precipitate or its basic form depending upon the precise conditions of preparation. These conclusions are closely parallel to those of Broderson and Rüdorff, on the corresponding compounds formed from mercuric bromide and ammonia.

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D(+)-*Apiose from the Monocotyledon,* Posidonia australis.

By D. J. BELL, F. A. ISHERWOOD, and NANCY E. HARDWICK.

(*With a Note on the Stereochemistry and Nomenclature.* By R. S. CAHN.)

[Reprint Order No. 5403.]

D(+)-Apiose has been identified as the main monosaccharide liberated, on mild acid hydrolysis, from both leaves and naturally "retted" residual fibres ("marine fibre") of *Posidonia australis* (Potamogetonaceae). This sugar has hitherto been known only as a component of the flavone glycosides derived from parsley (*Apium petrosilinum*, Umbelliferae). Two useful crystalline compounds of D-apiose are described, the di-*O*-*iso*propylidene derivative and the 2 : 5-dichlorophenylosazone. The latter contains no asymmetric centre and could be obtained from either the D- or the L-form of the sugar.

The stereochemistry and nomenclature of cyclic apiose derivatives are discussed.

As a sequel to the re-examination of the nature of the cellulose of the leaves and "residual fibre" of *Posidonia australis* by Bell (*J.*, 1952, 3649) unsuccessful attempts were made to isolate a xylan from the leaves of this plant. Dr. J. C. Earl, who kindly made his original notes available to us, had previously attempted, without success, to identify D-xylose among the products formed by treatment of the leaves and fibres with hot 2% sulphuric acid; neither the phenylosazone nor an identifiable oxidation product of D-xylose could be isolated.

We subjected both dried fresh leaves and residual fibres to treatment with hot 2% (w/v) sulphuric acid and examined the hydrolysate by paper chromatography, using aniline phthalate to reveal the sugar spots. Xylose, arabinose, and two bright yellow spots, in positions corresponding respectively to glucose and rhamnose, were observed.

It was therefore decided, as a preliminary to assaying the xylose in the hydrolysate, to attempt positive identification of the monosaccharides through their *O*-*iso*propylidene derivatives (Bell, *J.*, 1947, 1461). The product, obtained by treatment of the dried mixture of sugars with acetone containing 5% (v/v) of sulphuric acid, consisted largely of crystals unexpectedly insoluble in cold water. After recrystallisation from hot water, these crystals analysed exactly for a di-*O*-*iso*propylidenepentose but melted at 82°, being thus distinguished from similar derivatives of any of the "normal" pentoses. No unsubstituted hydroxyl groups could be detected.

When hydrolysed by N-acid this substance yielded a syrup which behaved chromatographically exactly as the "rhamnose" spot mentioned above. It did not, however, yield acetaldehyde on oxidation by periodate, nor could evidence be obtained by Edward and Waldron's procedure (*J.*, 1952, 3631) that the sugar contained a "secondary" deoxy-grouping (*i.e.*, $-CH_2-$).

Paper-chromatographic investigation under the exactly controlled conditions of Isherwood and Jermyn (*Biochem. J.*, 1951, **48**, 515) showed that the sugar was not an unbranched 2-hexulose, a hexose, a straight-chain pentose, or a 6-deoxyhexose. With ethyl acetate–pyridine–water (2 : 1 : 2) as solvent the R_F value was 0·40 while that of rhamnose was 0·38. The other 6-deoxyhexoses, in this solvent, have very different R_F values.

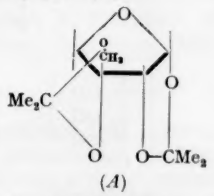
Analytically, although it did not yield furfuraldehyde on acid treatment, the sugar appeared to be without doubt a pentose and, from its high R_F value, probably existed in solution as a furanose. The ease of formation of a di-*O*-*iso*propylidene derivative suggested that examination of a paper chromatogram in presence of boric acid might provide a clue to its structure since boric acid is known to form complexes with vicinal hydroxyl groups attached to a five-membered ring (Böeseken, *Adv. Carbohydrate Chem.*, 1949, **4**, 189; Barker and Smith, *Chem. and Ind.*, 1954, 19). The R_F values given in the annexed Table show that the R_F of the unidentified sugar is markedly affected by boric acid. The only well-known pentose, not examined by Isherwood and Jermyn (*loc. cit.*), which might behave in this way, is apiose (cf. Hudson, *Adv. Carbohydrate Chem.*, 1949, **4**, 57), a sugar possessing a branched chain. The sugar from *Posidonia* and authentic D-apiose (prepared from apiin) showed identical behaviour on the paper chromatogram.

R_F values in *n*-butanol–water.

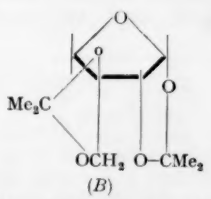
	Glucose	Rhamnose	Fucose	Galactose	*P. australis* sugar
Without boric acid ...	0·08	0·23	0·16	0·08	0·26
With boric acid	0·06	0·24	0·16	0·07	0·04

Proof that the sugar is in fact D(+)-apiose was afforded by the preparation from an authentic sample, isolated by controlled hydrolysis of apiin, of the di-*O*-*iso*propylidene derivative and the 2 : 5-dichlorophenylosazone. These were identical with the derivatives prepared from the *Posidonia* sugar, as were samples of the previously known *p*-bromophenylosazone (Vongerichten and Müller, *Ber.*, 1906, **39**, 235). It should be noted that osazones of apiose have lost their asymmetric centre and do not therefore distinguish between D- and L-isomers.

The structure of the di-*O*-*iso*propylidene derivative cannot yet be definitely stated. Arguing from the tendency of the *iso*propylidene radical to engage vicinal *cis*-hydroxyl groups, especially when one is a " reducing " hydroxyl group, it seems logical to assign positions 1 and 2 to one substituent. This would leave the remaining hydroxyl groups on positions 3 and 5 (which are not vicinal) to bear the second *iso*propylidene group. As discussed below, ring-formation in apiose results in the production of a new asymmetric carbon atom at position 3. At present we have no means of learning the configuration of this new asymmetric centre. We therefore suggest that the apiose derivative in question be for the present designated " probably 1 : 2-3 : 5-di-*O*-*iso*propylidene-D-apio-(D or L)-furanose," *i.e.* (*A*) or (*B*).



(*A*)



(*B*)

The form in which the apiose radicals are present in *Posidonia* is under investigation; it seems clear, since the sugar is liberated from the plant tissues only after acidic treatment, that they must be glycosidically bound. Hitherto this sugar has been known only in the form of the disaccharide-flavone glycoside apiin isolable from parsley (Hemming and Ollis, *Chem. and Ind.*, 1953, 85; cf. Hudson, *loc. cit.*). Our observations that, chromatographically, the sugar may be mistaken for rhamnose, and that it is present in a plant of a species totally different from an umbellifer, suggest that it may be more widely distributed than has hitherto been suspected. *Posidonia australis* does not appear to contain apiin.

Nothing is known of the biological behaviour of this sugar; we are unaware of any literature referring to tests done with micro-organisms. It is noteworthy that an adenoside of (+)-3-deoxyapiose (cordycepose) isolated by Bentley, Cunningham, and Spring (*J.*, 1951, 2299, 2301) has some antibiotic properties and that other branched monosaccharides occur in certain established antibiotics, *e.g.*, streptose in streptomycin (Lemieux and Wolfrom, *Adv. Carbohydrate Chem.*, 1948, **3**, 337) and (−)-mycarose in magnamycin (Regna, Hochstein, Wagner, and Woodward, *J. Amer. Chem. Soc.*, 1953, **75**, 4625). It is suggested, with all reserve, that the resistance to natural decomposition processes, so marked in the fibres of *Posidonia australis* and its close relative, *Zostera marina*, may be due to the presence of some derivative of D-apiose (cf. Winterbottom, South Australia Dept. Chemistry, 1917, Bull. No. 4, p. 28).

Stereochemistry and Nomenclature.*

The furanose forms of apiose present novel features of asymmetry and nomenclature.

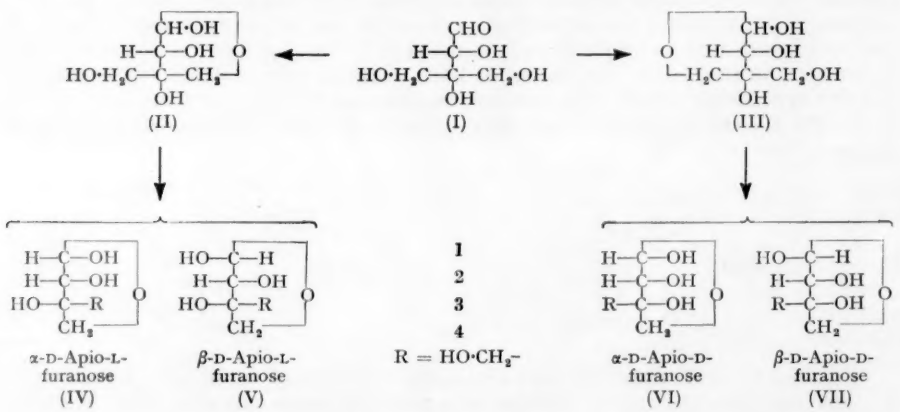
The *aldehydo*-form (I) of apiose may be called D-apiose (or, more specifically *aldehydo*-D-apiose), the prefix D being derived directly from the glyceraldehyde convention and the customary carbohydrate convention.

When furanose-ring formation takes place, as in (II) or (III), two further centres of asymmetry are created: one of these, that at position 1, is covered by the customary αβ nomenclature for glycosidic anomers; the second, that at position 3, is not covered by the normal rules of carbohydrate nomenclature (*J.*, 1952, 5108).

It will be wise always to write apiose projection formulae in the conventional way, with the primary alcoholic group which is involved in ring formation at the bottom (if the oxygen bridge starts vertically from position 1, it is immaterial whether the oxygen atom is written to the left or to the right since, in so far as the projection formulæ have pictorial meaning, the ring lies behind the plane of the paper). Thus the formula (II) should be re-written as (IV) and (V), and the formula (III) as (VI) and (VII).

Numbering should be 1 to 4, from the glucosidic position to the other end of the furanose ring, with the free CH_2·OH group numbered 5.

According to the direction of ring-closure, D-apiose will give one or more of the four isomers (IV)—(VII). L-Apiose similarly gives the mirror images of these, a total of eight



optically active individuals, as required for a compound containing three different asymmetric centres.

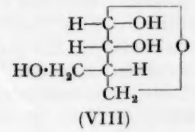
According to the customary nomenclature of carbohydrates (*ibid.*, rule 5) the con-

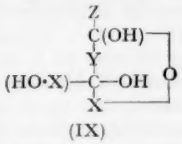
* The Chemical Society's Carbohydrate Nomenclature Sub-Committee has not yet considered branched-chain sugars. The appearance of the Editor's name as an author must not be construed as committing the Society to the nomenclature proposed in this paper.

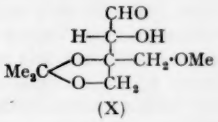
figurational prefix D or L follows the asymmetry of the highest-numbered asymmetric atom. But the *aldehydo*-form (I) of D-apiose then generates two D-furanose forms (VI and VII) and two L-furanose forms (IV and V); similarly, *aldehydo*-L-apiose generates two L- and two D-furanose forms. The generic relations of the individuals would thus be obscured. For example, by classical principles, (II; = III + IV) might be termed αβ-L-*threo*apiose, whilst (III; = VI + VII) might be termed αβ-D-*erythro*apiose, yet both are derived from *aldehydo*-D-apiose (I).

We therefore suggest a new form of nomenclature for this sugar. Let " D-apio " refer always to the asymmetry of the open-chain form (I), *i.e.*, to position 2. When this form cyclises, " furanose " should be added to the stem, as customary, but now together with a second D defining the stereochemistry at position 3, giving D-apio-D-furanose, etc. Addition of the customary prefixes α, β completes the names, which then are as under the formulæ (IV)—(VII). In these designations the three stereochemical prefixes denote, in order, the configuration at positions 1, 2, and 3. The mirror image of a particular isomer is that in which all three stereochemical prefixes are simultaneously reversed.

Bentley, Cunningham, and Spring (*loc. cit.*) encountered a similar case with cordycepose, a 3-deoxyapiose (*e.g.*, VIII), but in their work did not need a precise stereochemical nomenclature. Since there is no hydroxyl group at position 3 there is no firm convention or rule by which to assign a prefix *threo* or *erythro*, or a symbol D or L, to the name cordycepose in connexion with the stereochemistry of its furanose forms. Thus it is preferable to designate the furanose forms of cordycepose in terms of 3-deoxyapiose; the nomenclature suggested above is adequate also for the 3-deoxy-derivative.


(VIII)


(IX)


(X)

The specific case of apiose can be generalised by the expression (IX), the essential features calling for the revised nomenclature being that ring closure creates new asymmetry at a carbon atom which bears a higher number than that of any other asymmetric atom in the chain. Apiose is (IX) in which X = CH_2, Y = CH·OH, and Z = H, and the nomenclature proposed will deal adequately with some analogous cases; but others can be conceived, *e.g.*, (X), in which other considerations may ensue. Accordingly the nomenclature proposed for apiose (and cordycepose) should be regarded as an interim step until more branched-chain sugars presenting this particular problem have been isolated; it will then be clearer whether the classical carbohydrate conventions can be adequately modified to meet practical demands, or whether recourse must be had to one of the general schemes (cf. Cahn and Ingold, *J.*, 1951, 612; Klyne, *Chem. and Ind.*, 1951, 1022; McCasland, cited by Patterson, *Chem. Eng. News*, 1954, 32, 434).

Experimental

Evaporations were done under reduced pressure below 40°.

Hot Acid Extraction of Posidonia *Leaves.*—To 100 g. of air-dried *Posidonia* leaves (water content 10%) were added N-sulphuric acid and water in proportions such that the final acid concentration (by titration) was ~0·4N. The total volume of liquid was 850 ml. The whole was then heated at 100° for 1 hr., cooled, and filtered; the residue was well pressed and washed twice with water. After neutralisation by barium carbonate, the filtered solution and washings were shaken with charcoal and again filtered, through Celite and charcoal. The filtrate, acidified with acetic acid, was evaporated. (This preliminary acidification was found to be essential to prevent aldose–ketose interconversion.)

Samples of " residual fibres " were treated in the same way.

Paper-chromatographic Examination of the Hydrolysate.—Since the neutralised hydrolysates contained inorganic salts which interfered with direct chromatographic examination numerous trials were done before a satisfactory procedure was found. (It was early noted that D-apiose

is remarkably sensitive to alkali; traces of soluble alkali in barium carbonate preparations cause the subsequent production of two spots on the chromatogram, presumably due to aldose–ketose transformation.) In view of the observations of Hulme (*Nature*, **1953**, **171**, 610) and of Rebenfeld and Pacsu (*J. Amer. Chem. Soc.*, **1953**, **75**, 4371) regarding the destructive and isomerising effects of strongly basic resins, it was considered advisable not to attempt deionisation by such means. Direct chromatography of the acid hydrolysate by Gaillard's method (*Nature*, **1953**, **171**, 1160) was found to give very satisfactory results. Using as solvent benzene–butanol–pyridine–water (1 : 5 : 3 : 3), developing for 16 hr. at room temperature, and spraying with aniline hydrogen phthalate (Partridge, *Nature*, **1948**, **164**, 443) gave the results tabulated on p. 3703 for material from both leaves and fibres.

Isolation of the Di-O-iso*propylidene Derivative of* D-*Apiose* (cf. Bell, **1947**, *loc. cit.*).—The mixture of sugars, obtained by 0·4N-acid treatment, was dissolved in water (50 ml.) and evaporated in presence of Celite (4 g.). The resulting mass, after drying at 0·05 mm. over phosphoric oxide, was agitated with dry acetone (300 ml.) containing 5% (v/v) of sulphuric acid for 6 hr. at room temperature. The final product was largely crystalline. Recrystallised from water containing a trace of ammonia, needles or plates were found with m. p. 81—83° and $[\alpha]_D^{19}$ +56·4° (*c*, 3·2 in EtOH) (Found: C, 57·5; H, 7·7. $C_{11}H_{18}O_5$ requires C, 57·4; H, 7·9%). In attempts to acetylate this material it was recovered unchanged. Yields were: from leaves, 2·6% (rather less from a second batch); from fibre, 2·5%; from water-extracted leaves, <0·1%.

Authentic D(+)-apiose was treated as above. The product had m. p. and mixed m. p. 81—83°, $[\alpha]_D^{19}$ +55·6° (*c*, 1·35 in EtOH) (Found: C, 57·5; H, 7·7%).

Apiose 2 : 5-*Dichlorophenylosazone.*—To the sugar (75 mg.) obtained after acid hydrolysis of the di-*O-iso*propylidene derivative (obtained from leaves), were added water (1 ml.), 2 : 5-dichlorophenylhydrazine (300 mg.), ethanol (1 ml.), 8N-acetic acid (2 ml.), and sufficient sodium acetate to give a final pH of 4·5. The mixture was heated (~100°) for 45 min. A yellow solid separated; as this was considered possibly to be a hydrazone it was dissolved by dropwise addition of ethanol. After heating of the solution for a further 5 min. and cooling, the yellow product was collected and recrystallised from ethanol to which water was added dropwise.

Apiose 2 : 5-*dichlorophenylosazone* (needles) had m. p. 188·5—190·5°, not depressed on admixture with material prepared from authentic D-apiose (Found: C, 44·5; H, 3·4; N, 12·1; Cl, 30·3. $C_{17}H_{16}O_3N_4Cl_4$ requires C, 43·8; H, 3·4; N, 12·0; Cl, 30·5%). Authentic apiose 2 : 5-dichlorophenylosazone had m. p. 187—188° (Found: C, 44·3; H, 3·8; N, 13·1; Cl, 32·3%).

Apiose p-*Bromophenylosazone.*—This was prepared essentially as described for the dichloro-derivative. After heating of the reaction mixture for 1·5 hr., the resulting crystals, recrystallised from aqueous alcohol, had m. p. 209·5—210·5° (corr.). Vongerichten and Müller (*loc. cit.*) give m. p. 211—212°. Yields of both ozazones were very satisfactory.

As regards one of us (F. A. I.) the work described in this paper was carried out as part of the programme of the Food Investigation Organisation of the Department of Scientific and Industrial Research; Mr. F. C. Barrett performed much of the chromatographic work described. We are grateful to Dr. H. B. S. Womersley of the Botany Department, Adelaide University, for generous supplies of *Posidonia* leaves and fibres. One of us (N. E. H.) is indebted to the University of Western Australia for a Hackett Studentship and to Girton College, Cambridge, for an Ethel Sargant Studentship.

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The Decomposition of αα′-Azoisobutyronitrile in Solution.

By J. C. Bevington.

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The decomposition of αα′-azo*iso*butyronitrile in dilute solutions has been studied by estimating the tetramethylsuccinodinitrile and *iso*butyronitrile formed by combination and disproportionation respectively of the 2-cyano-2-propyl (1-cyano-1-methylethyl) radicals produced from the azo-compound. Dilute solutions of the azo-compound, labelled with ^{14}C, have been used, their concentrations being similar to those when the compound is used as an initiator of polymerizations. The products have been estimated by the method of isotopic dilution. In the early stages of the decomposition, disproportionation occurs more frequently than combination, but as decomposition proceeds combination becomes predominant.

Bevington, Bradbury, and Burnett (*J. Polymer Sci.*, 1954, **12**, 469) described a new method for determination of the rates of initiation in radical polymerizations; it involved the use of an initiator which can be estimated with accuracy in very small concentrations so that the exact amount of initiator combined in the polymer can be determined. This requirement is met if the initiator is labelled with a radioactive isotope; the initiator most frequently used has been αα′-azo*iso*butyronitrile (referred to as AZDN in Tables of results) labelled with ^{14}C on the methyl groups. If the rate of decomposition of the initiator is known, it is possible to calculate the efficiency with which radicals formed from it initiate polymerization. It has been found that for a number of systems this efficiency is well below 100%, frequently being near 50%; a number of American workers (see, *e.g.*, Arnett and Peterson, *J. Amer. Chem. Soc.*, 1952, **74**, 2031) have concluded that in many cases the efficiency is close to 100%.

A way to decide between these conflicting views on initiator efficiency would be to detect and estimate products formed from those radicals which do not initiate polymerization. Analysis by conventional methods is impracticable because of the small weights of the substances involved and the complexity of the mixture. The analysis can be performed satisfactorily by using a labelled initiator and the method of isotopic dilution.

The most thorough study of the products resulting from the decomposition of αα′-azo-*iso*butyronitrile is that of Bickel and Waters (*Rec. Trav. chim.*, 1950, **69**, 1490). Their work suggests that almost all the wasted 2-cyano-2-propyl radicals would combine to give tetramethylsuccinodinitrile (referred to as TMSDN in Tables of results). It has been found that during the polymerization of styrene at 60° initiated by the thermal decomposition of αα′-azo*iso*butyronitrile, the dinitrile is indeed formed but it is accompanied by an appreciable quantity of *iso*butyronitrile (referred to as IBN in the Tables); this substance is probably formed by the disproportionation of pairs of the radicals. If allowance is made for both combination and disproportionation of wasted radicals, it is confirmed that the efficiency is well below 100%. In view of the difference between the nature of the products from the interaction of the radicals in these experiments and in those of Bickel and Waters (*loc. cit.*), a study of the decomposition of αα′-azo*iso*-butyronitrile in inert solvents was undertaken.

Experiments were conducted in benzene, toluene, and carbon tetrachloride under conditions similar to those used in the experiments with styrene. Other experiments were performed under the conditions used by Bickel and Waters (*loc. cit.*); further experiments were carried out in an attempt to correlate the two sets of results.

Experimental

Materials.—αα′-Azo*iso*butyronitrile labelled with ^{14}C was prepared in connection with previous work (Bevington, Melville, and Taylor, *J. Polymer Sci.*, 1954, **12**, 449). Solvents were dried and redistilled before use. Inactive tetramethylsuccinodinitrile was prepared (Bickel and Waters, *loc. cit.*) and recrystallized from ethanol. Inactive *iso*butyronitrile was made by dehydration of *iso*butyramide and purified by distillation.

Reaction Mixtures.—A weighed amount of the labelled azo-compound and a known volume of solvent were introduced into the reaction vessel. When necessary the solution was degassed on the vacuum line and the vessel was sealed.

Isolation of Products.—The reaction mixture was mixed with known weights of inactive tetramethylsuccinodinitrile and *iso*butyronitrile dissolved in ethanol. The solution was separated into a liquid and a solid portion by distillation at low temperatures on the vacuum line. From the solid consisting of tetramethylsuccinodinitrile and a much smaller weight of undecomposed azo-compound, pure dinitrile was recovered by repeated recrystallization from ethanol. The liquid was redistilled and then the *iso*butyronitrile contained in it was converted into the amide through the acid and the acid chloride. The amide was recrystallized from benzene.

Assay Procedure.—The specific activities of the active substances were compared by the method of gas-counting (Bevington, Melville, and Taylor, *loc. cit.*; Bevington, Guzman, and Melville, *Proc. Roy. Soc.*, **1954**, *A*, **221**, 437), the carbon dioxide being obtained by wet combustion. In the experimental results, corrected counting rates in counts per minute (c/m.) for a standard filling of the counter are quoted. The counting rate is directly proportional to the $^{14}C : {}^{12}C$ ratio in the material oxidized.

Calculation of Results.—The weight of product formed in the decomposition is calculated from the known weight of carrier and the counting rates of the diluted product and the original azo-compound.

Results. Tests on Purification Procedures.—It is an essential of the method that tetramethylsuccinodinitrile and *iso*butyramide of high purity should be recovered from the mixture, and tests on the efficiencies of the purifications were made. Mixtures of labelled αα′-azo*iso*butyronitrile and much larger weights of unlabelled tetramethylsuccinodinitrile were made, and the latter was recovered by recrystallization from ethanol. After each crystallization the dinitrile was assayed; any activity found in it must have been due to incomplete removal of the azo-

TABLE 1.

	Test 1	Test 2	Test 3
Wt. of AZDN (96,500 c/m.) (mg.)	10·0	14·7	34·8
Wt. of inactive TMSDN (mg.)	1441	769	1257
Calc. c/m. for no separation	551	1505	2170
Obs. c/m. for TMSDN after successive crystallizations...	35, 13	64, 18·5	317, 32, 19

compound, to decomposition during recrystallization, or to exchange reactions. Tests showed that after three crystallizations the amount of activity in the dinitrile was small. The results in Table 1 indicate that in experiments where tetramethylsuccinodinitrile of fairly low activity is separated from a much smaller weight of αα′-azo*iso*butyronitrile of high activity by repeated crystallization, a small correction must be made to the observed activity of the dinitrile even after three crystallizations. The magnitude of this correction appears to be small and it can be estimated from the results of these test separations.

In an experiment in which labelled *iso*butyramide was isolated, the product was recrystallized three times and assayed after each crystallization. The counting rates at the three stages were 384, 387, and 373; the m. p. of the product was sharp after the first crystallization. These results show clearly that the procedure adopted for purification of this compound was satisfactory.

When the alcoholic solution containing active materials and carriers is separated into solid and liquid fractions, it is possible that active αα′-azo*iso*butyronitrile and tetramethylsuccinodinitrile might sublime and be mixed with the *iso*butyronitrile in the liquid fraction. The amide prepared from this nitrile is recrystallized and the test described above shows that the tetramethylsuccinodinitrile (or products derived from it) are eliminated; if αα′-azo*iso*butyronitrile is present in the *iso*butyronitrile however it would be decomposed during the hydrolysis of the nitrile and the weight of nitrile found would not be that produced in the original decomposition.

In all experiments the distillate from the vacuum-distillation was redistilled, but in one case about ½ g. of inactive tetramethylsuccinodinitrile and about ½ g. of inactive azo-compound were added to the liquid before the second distillation. If sublimation of αα′-azo*iso*butyronitrile is serious, the error in this experiment would result in a decrease in the specific activity of the recovered *iso*butyramide and therefore in an apparent decrease in the amount of active *iso*butyronitrile present in the original liquid. The conditions were chosen so that they were favourable for sublimation, the dry solid being left connected to the cold trap for about 30 min.

In this experiment it was found that 43·6% of the $CN{\cdot}CMe_2{\cdot}$ radicals apparently underwent combination, whereas in a similar experiment carried out in the normal manner, this percentage was 35. The difference was due to the fact that in the special experiment the specific activity of the amide was less than in the routine experiment. Clearly, sublimation occurs to some extent, but even in an experiment in which its effect was deliberately made much larger than usual, the effect upon the final result was not very large; for this reason sublimation is neglected in calculation of results. Any errors due to sublimation cannot affect analyses for tetramethylsuccinodinitrile, and in all cases there was agreement between the amount of azo-compound decomposed, calculated from the known rate of decomposition, and the amount calculated from the found weights of products.

Experiments at 60°.—Solutions of αα′-azo*iso*butyronitrile in benzene, toluene, and carbon tetrachloride were treated in ways similar to the solutions of initiator in styrene. The concentration of the azo-compound was in the region of 5 mg./ml., and the solutions, which were free from air, were kept at 60° for periods of 5—9 hr. so that between 15% and about 25% of the azo-compound was decomposed. These experiments are summarized in Table 2.

TABLE 2.

Expt.:	No. 1	No. 2	No. 3	No. 4	No. 5
Wt. of AZDN (mg.)	25·5	21·3	26·1	20·2	20·9
Vol. of solvent (ml.) †	6·0B	4·3T	4·8B	5·1T	4·0C
Time at 60° (hr.)	6·0	8·75	6·5	9·0	4·75
Calc. % of AZDN decomposed	18·5	25·9	20·0	26·5	15·0
Wt. of TMSDN (mg.) found	1·42	1·75	1·56	*	0·825
Wt. of IBN (mg.) found	1·24	*	*	1·36	0·80
AZDN equiv. of TMSDN (mg.)	1·71	2·11	1·88	*	0·99
AZDN equiv. of IBN (mg.)	2·95	*	*	3·24	1·88
% of radicals combining	36·7	38·2	36·0	39·5	34·5

* No analysis performed. † B = Benzene; T = toluene; C = carbon tetrachloride.

The velocity constant for the first-order decomposition of αα′-azo*iso*butyronitrile at 60° is taken as $9{\cdot}52 \times 10^{-6}$ sec.$^{-1}$; this value, taken from Bawn and Mellish's data (*Trans. Faraday Soc.*, 1951, **47**, 1216), is in reasonable agreement with values of other workers. It is assumed that *iso*butyronitrile results from the disproportionation of pairs of radicals; this is discussed later. Calculations of the percentages of radicals combining are based on the calculated amount of αα′-azo*iso*butyronitrile decomposed except where analyses for both tetramethylsuccinodinitrile and *iso*butyronitrile were performed; in these cases the results of the two analyses were used in the calculations.

In another series of experiments solutions of the azo-compound in benzene (about 5 mg./ml.) were degassed and kept at 60° for 2—115 hr., so that the percentage decomposed ranged from about 6% to about 98%. Results are presented in Table 3.

TABLE 3.

Expt.:	No. 6	No. 7	No. 8	No. 9	No. 10
Wt. of AZDN (mg.)	16·1	28·4	10·4	15·3	10·7
Vol. of benzene (ml.)	3·1	6·0	2·0	3·0	2·0
Time at 60° (hr.)	2·0	3·55	24·5	43·25	114·25
Calc. % AZDN decomposed	6·54	11·4	56·8	77·3	98·1
Wt. of TMSDN (mg.) found	0·195	0·60	2·36	5·73	5·97
Wt. of IBN (mg.) found	0·270	0·82	0·80	0·98	0·45
AZDN equiv. of TMSDN (mg.)	0·24	0·72	2·85	6·91	7·20
AZDN equiv. of IBN (mg.)	0·64	1·94	1·90	2·33	1·08
% of radicals combining	27·3	27·0	60·0	74·8	87·0

In order to see if the decomposition is influenced by air, a solution containing 28·4 mg. of αα′-azo*iso*butyronitrile in 6·0 ml. of toluene was kept at 60° for 3·5 hr. with free access of air (Expt. No. 11) and afterwards 0·61 mg. of tetramethylsuccinodinitrile and 0·82 mg. of *iso*butyronitrile were found in the solution, indicating that 28·0% of the radicals underwent combination. The calculated weight of αα′-azo*iso*butyronitrile decomposed is 3·25 mg., and the weight equivalent to the found tetramethylsuccinodinitrile and *iso*butyrinitrile was 2·68 mg. The results of this experiment are closely similar to those of Expt. No. 7, showing that the decomposition is hardly affected by air.

Some experiments (see Table 4) were performed at 60° in the absence of air but in the presence of either tetramethylsuccinodinitrile or *iso*butyronitrile, both of which are products of the decomposition.

Solutions of αα′-azo*iso*butyronitrile in pure styrene were degassed and kept at 60°; the polymers were recovered by precipitation in alcohol. In Expt. No. 15 tetramethylsuccinodinitrile and *iso*butyronitrile were contained in the alcohol; in Expt. No. 16 the solution of

TABLE 4.

	Expt.	No. 12	No. 13	No. 14
Wt. of AZDN (mg.)	In reaction mixture	26·7	20·6	16·2
Vol. of benzene (ml.)	In reaction mixture	5·0	0	4·2
Wt. of TMSDN (mg.)	In reaction mixture	553·8	0	0
Wt. of IBN (mg.)	In reaction mixture	0	3090	695
Time at 60° (hr.)		23·75	23·75	19·17
Wt. of TMSDN (mg.) found	Formed in decomposn.	6·73	3·25	2·28
Wt. of IBN (mg.) found	Formed in decomposn.	1·49	0·28	0·32
AZDN equiv. of TMSDN (mg.)		8·11	3·92	2·75
AZDN equiv. of IBN (mg.)		3·54	0·67	0·77
% decomposn. of AZDN by calcn.		55·7	55·7	48·1
% decomposn. of AZDN from products		43·6	22·3	22·3
% radicals combining		69·6	85·2	78·1

polymer in monomer was mixed with benzene containing the carriers before precipitation. Samples of pure tetramethylsuccinodinitrile and *iso*butyramide were recovered by the methods described already. The relevant features of two experiments are shown in Table 5; these and similar experiments will be discussed in another paper. It is evident that the relative importances of combination and disproportionation in the interaction of pairs of $CN{\cdot}CMe_2{\cdot}$ radicals is about the same in styrene as in benzene, toluene, and carbon tetrachloride.

TABLE 5.

	Expt. No. 15	No. 16
Wt. of AZDN (mg.)	31·2	25·0
Vol. of styrene (ml.)	6·42	6·90
AZDN decomposed (%), calc.	15·3	5·7
Wt. of TMSDN (mg.) found	0·39	0·18
Wt. of IBN (mg.) found	0·46	0·18
AZDN equiv. of TMSDN (mg.)	0·47	0·22
AZDN equiv. of IBN (mg.)	1·09	0·43
% wasted radicals combining	30·1	33·8

TABLE 6.

	Expt. No. 17	No. 18
Wt. of AZDN (mg.)	277·3	7·75
Vol. of toluene (ml.)	1·4	2·0
Time of reflux (hr.)	3·20	3·67
Wt. of TMSDN (mg.) found	186·8	4·81
Wt. of IBN (mg.) found	8·77	0·20
AZDN equiv. of TMSDN (mg.)	225·3	5·80
AZDN equiv. of IBN (mg.)	20·8	0·47
% radicals combining	91·5	92·5

Experiments at 110°.—Solutions of labelled αα′-azo*iso*butyronitrile in toluene were refluxed in air for about 3½ hr., by which time decomposition of the azo-compound was almost complete. The conditions for these experiments approximate to those in Bickel and Waters's experiments (*loc. cit.*). Results are summarized in Table 6.

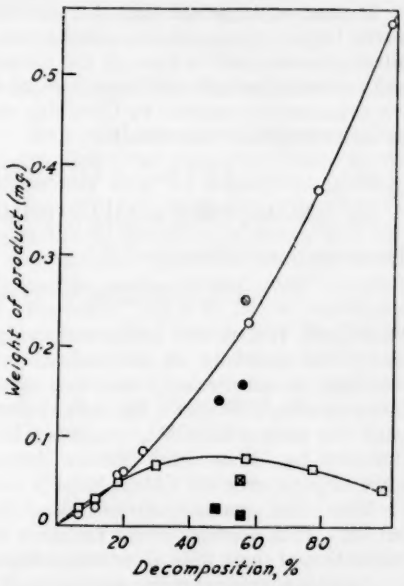
DISCUSSION

The *iso*butyronitrile produced in the decomposition of αα′-azo*iso*butyronitrile in solvents containing hydrogen could arise either from the disproportionation of pairs of $CN{\cdot}CMe_2{\cdot}$ radicals or from a reaction in which a radical abstracted a hydrogen atom from a molecule of the solvent. The fact that the quantity of *iso*butyronitrile produced during decomposition in carbon tetrachloride is very similar to the quantities produced in similar experiments in benzene and toluene shows that the hydrogen-abstraction process is of little significance. There is clear evidence that transfer to αα′-azo*iso*butyronitrile is of negligible importance in polymerization reactions (see Bevington, Melville, and Taylor, *loc. cit.*), so it is unlikely that $CN{\cdot}CMe_2{\cdot}$ radicals would abstract hydrogen atoms from the azo-compound at an appreciable rate. In all experiments in benzene, toluene, and carbon tetrachloride, the weight of αα′-azo*iso*butyronitrile decomposed, calculated from Bawn and Mellish's data (*loc. cit.*), was a little greater than the weight calculated from the weights of tetramethylsuccinodinitrile and *iso*butyronitrile. This difference may be due in part to the chosen velocity constant's being slightly wrong and in part to the fact that some of the radicals disappear by reaction with the methacrylonitrile produced during the decomposition; Bickel and Waters (*loc. cit.*) found evidence that this reaction actually occurs.

Expts. No. 17 and 18 confirm that in toluene at about 110° the major product from the decomposition of αα′-azo*iso*butyronitrile is the combined product. On the other hand,

the experiments reported in Table 2 show that at small extents of decomposition at 60° disproportionation of the radicals occurs more frequently than combination. The conditions under which the experiments of Table 2 were performed differ in a number of respects from those prevailing in Expts. No. 17 and 18; Table 3 shows that the differences in results can be ascribed to differences in the extent of decomposition. At 60°, as decomposition proceeds, combination appears to become increasingly important.

The variation in the relative quantities of tetramethylsuccinodinitrile and *iso*butyronitrile during decomposition might be explained by supposing that ordinarily αα′-azo*iso*butyronitrile contains two types of molecule the less stable of which gives radicals which tend to undergo disproportionation; the more stable and more abundant form would be assumed to give radicals prone to undergo combination. If this were the case the observation that the two modes of inter-radical reaction vary in importance with the extent of decomposition could be explained qualitatively. This hypothesis is at variance with the



The weights of tetramethylsuccinodinitrile and iso*butyronitrile formed at various stages in the decomposition of* 1 *mg. of* αα′-azo*isobutyronitrile.*

○ and □ refer to tetramethylsuccinodinitrile and *iso*butyronitrile respectively for experiments in benzene and toluene; ● and ■ to these substances for experiments in the presence of *iso*butyronitrile; ⊗ and ⊠ to these substances for an experiment performed in the presence of tetramethylsuccinodinitrile.

fact that it is generally agreed that the decomposition of αα′-azo*iso*butyronitrile has no obvious anomalies in the rate–time relationships. In addition, closer examination shows that this hypothesis does not fit the experimental results.

From the results in Tables 2 and 3, the weights of products formed at various stages in the decomposition of 1 mg. of the azo-compound can be calculated. From Fig. 1 it is seen that the weight of *iso*butyronitrile rises to a maximum and then falls off; also the weight of tetramethylsuccinodinitrile is not a linear function of the extent of decomposition. If the hypothesis already discussed were true, the amount of *iso*butyronitrile should increase during the early stages of the reaction but subsequently it should increase only very slowly or remain stationary.

The variations in the relative proportions of tetramethylsuccinodinitrile and *iso*butyronitrile with the extent of decomposition of the azo-compound and the disappearance of *iso*butyronitrile in the later stages of the decomposition could be explained if *iso*butyronitrile and methacrylonitrile, the two products of disproportionation, could interact to form tetramethylsuccinodinitrile fairly slowly at 60°. If this were the case, the amount of *iso*butyronitrile found in the reaction mixture would rise to a maximum and then would gradually decrease as it reacted with methacrylonitrile; also the weight of tetramethyl-

succinodinitrile would not be a linear function of the extent of decomposition. By this hypothesis, the actual tendencies of the radicals for disproportionation and combination should be measured by the relative yields of the two types of products in the early stages of the decomposition; by this criterion about 30% of the inter-radical reactions occur by combination.

Consider the results at 50% decomposition; by extrapolation of the results obtained at small extents of decomposition the expected weights of tetramethylsuccinodinitrile and *iso*butyrontrile are 0·100 and 0·126 mg. respectively. The found weights of these products are 0·190 and 0·079 mg. If the *iso*butyronitrile which appears to have been lost reacted with methacrylonitrile to give tetramethylsuccinodinitrile, 0·095 mg. of the latter would be produced. This corresponds closely with the difference between the found and expected weights of the dinitrile. The differences between the calculated and observed weights of tetramethylsuccinodinitrile and *iso*butyronitrile can be correlated similarly at other stages in the decomposition.

It must be supposed that the postulated reaction of *iso*butyronitrile and methacrylonitrile to give tetramethylsuccinodinitrile occurs only in the presence of αα′-azo*iso*butyronitrile, because only a trace of the dinitrile was found after a mixture of *iso*butyronitrile and methacrylonitrile had been kept at 60° for several days. This probably means that the reaction is promoted by $CN{\cdot}CMe_2{\cdot}$ radicals. The following sequence of reactions can be used to explain these results :

(i) $$CN{\cdot}CMe_2{\cdot} + CH_3{\cdot}C(CN){:}CH_2 \longrightarrow CN{\cdot}CMe_2{\cdot}CMe(CN){\cdot}CH_2{\cdot}$$

(ii) $$CN{\cdot}CMe_2{\cdot}CMe(CN){\cdot}CH_2{\cdot} + CHMe_2{\cdot}CN \longrightarrow CN{\cdot}CMe_2{\cdot}CMe_2{\cdot}CN + CN{\cdot}CMe_2{\cdot}$$

These reactions add up to

$$CH_3{\cdot}C(CN){:}CH_2 + CHMe_2{\cdot}CN \longrightarrow CN{\cdot}CMe_2{\cdot}CMe_2{\cdot}CN$$

Bickel and Waters (*loc. cit.*) found evidence that radicals attacked methacrylonitrile but wrote the structure of the radical produced as $(CH_3)_2C(CN){\cdot}CH_2{\cdot}C(CN)(CH_3){\cdot}$. This structure would normally be taken as more likely than the one written in equation (i). Other reactions in which the radical produced in (i) might engage are: (iii) Combination with the radical $CN{\cdot}CMe_2{\cdot}$ to give $CN{\cdot}CMe_2{\cdot}CMe(CN){\cdot}CH_2{\cdot}CMe_2{\cdot}CN$; this product was detected by Bickel and Waters (*loc. cit.*). (iv) Disproportionation with the radical $CN{\cdot}CMe_2{\cdot}$ to give $CN{\cdot}CMe_2{\cdot}CMe_2{\cdot}CN + CN{\cdot}CMe{:}CH_2$. (v) Combination with another of its kind; the structure of the radical does not permit of disproportionation in the interaction. This reaction would probably not be of very great importance because the concentration of these radicals would presumably be very low.

On this suggested reaction scheme, it is possible to predict the effect of *iso*butyronitrile upon the apparent production of tetramethylsuccinodinitrile during the decomposition of αα′-azo*iso*butyronitrile. If the $CN{\cdot}CMe_2{\cdot}$ radical in (i) is derived directly from the labelled initiator, it has a high specific activity; it is converted, however, into a radical having very low specific activity because the *iso*butyronitrile engaged in reaction (ii) is composed of a very small weight of material of high activity mixed with a much larger weight of inactive carrier. Some of the radicals of low specific activity combine to give tetramethylsuccinodinitrile of low activity; an error is introduced into the analysis for this substance because it is assumed that all the dinitrile present before the addition of carrier has a high specific activity. The Figure shows that the amount of tetramethylsuccinodinitrile found by analysis in these circumstances is definitely lower than the amount formed in benzene solutions. No satisfactory explanations can be advanced for the very marked reductions in the amounts of *iso*butyronitrile found when the decompositions were performed in the presence of inactive tetramethylsuccinodinitrile or *iso*butyronitrile.

The author thanks Professor H. W. Melville, F.R.S., for his interest in this work.

The Department of Chemistry,
The University, Birmingham, 15. [*Received, May 26th*, 1954.]

The Chemistry of Fungi. Part XXIII. Tumulosic Acid.*

By L. A. Cort, R. M. Gascoigne, J. S. E. Holker, B. J. Ralph, Alexander Robertson, and J. J. H. Simes.

[Reprint Order No. 5414.]

A mixture of acids, isolated from artificially grown *Polyporus tumulosus* Cooke, *P. australiensis* Wakefield, or *Poria cocos* Wolf, difficult to separate, has been shown to contain a doubly unsaturated dihydroxy-monobasic acid, tumulosic acid, $C_{31}H_{50}O_4$, and its dehydro-derivative, $C_{31}H_{48}O_4$, each of which contains a reactive double bond present in a vinylidene group.

Tumulosic and dehydrotumulosic acid, respectively, have been converted into methyl eburico-7 : 9(11)-dien-21-oate (III; R = H), and 3β : 16α-dihydroxyeburico-7 : 9(11)-dien-21-oate (VII; R = Me, R′ = R″ = H) and its diacetate (VII; R = Me, R′ = R″ = Ac). The position of the reactive vinylidene group in tumulosic acid has been determined and a structure (XII) for the compound deduced.

In an appendix, acids from strains of *Poria cocos* (Schw.) Wolf are reported.

In Part XIV (*J.*, 1950, 3380) the identification of some of the water-soluble metabolites produced by the wood-rotting Basidiomycete fungus *Polyporus tumulosus* Cooke grown on an artificial medium was described and, simultaneously with the subsequent investigations on eburicoic acid (Part XVI, *J.*, 1951, 2346; Part XVII, *J.*, 1953, 1830; Part XVIII, *J.*, 1953, 2414; Part XIX, *J.*, 1953 2422), an examination of the mycelial products of this fungus led to the isolation of ergosterol and a new unsaturated, monobasic, tetracylic, dihydroxy-acid, $C_{31}H_{50}O_4$, for which the name tumulosic acid is provisionally adopted. Like eburicoic acid from some species of Basidiomycete fungi (Part XVI, *loc. cit.*) tumulosic acid is accompanied by a closely related compound characterised by selective ultra-violet absorption maximum at 243 mμ with associated subsidiary peaks at 236 and 251 mμ. The compound which shows this spectral property and occurs together with eburicoic acid in some fungi has been shown to be dehydroeburicoic acid (Part XVII, *loc. cit.*) and it appeared probable that in the case of tumulosic acid the accompanying acid with $\lambda_{max.}$ 243 mμ was dehydrotumulosic acid. Like the natural mixture of eburicoic and dehydroeburicoic acid the mixed acids from *P. tumulosus* Cooke proved extremely difficult to separate. However, by exhaustive chromatography of the mixture of the acetylated acids sufficient pure tumulosic acid † has been obtained for characterisation and for preliminary experiments. The isolation of dehydrotumulosic acid from the natural mixture has not so far been successful. A closely similar mixture of tumulosic and dehydrotumulosic acid has also been isolated from the mycelium of *Polyporus australiensis* Wakefield grown on the artificial medium, and from the naturally occurring sporophores of this species, but a separation of the mixture was not attempted; its identity was established by the preparation of derivatives of the mixed acids and the comparison of their infra-red absorption with the absorption of corresponding derivatives of the mixture obtained from *P. tumulosus*.

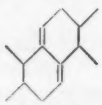
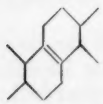
Two hydroxyl groups are present in tumulosic acid since the acid and its methyl ester, respectively, form *O*-diacetyltumulosic acid and methyl *O*-diacetyltumulosate, each of which on catalytic hydrogenation absorbs a mol. of hydrogen, giving the corresponding dihydro-compounds. The dihydro-derivatives give yellow colours with chloroformic tetranitromethane, indicating the presence of a second and unreactive double bond. On oxidation with lead tetra-acetate, the diol formed from methyl *O*-diacetyltumulosate with osmium tetroxide gave formaldehyde, whereas methyl *O*-diacetyldihydrotumulosate was not oxidised under these conditions. Consequently the reactive double bond of tumulosic

* Part XXII, *J.*, 1954, 1432.

† The mixture of tumulosic and dehydrotumulosic acid was first isolated by Dr. B. J. Ralph (Thesis, Liverpool, 1949), and the isolation of tumulosic acid was reported by Dr. R. M. Gascoigne (Thesis, Liverpool, 1951). A. R.

acid is present in a vinylidene group and in agreement with this conclusion the infra-red spectrum of methyl *O*-diacetyltumulosate exhibits a peak at 891 cm.$^{-1}$ whereas the corresponding dihydro-derivative does not show selective absorption in the 12 μ region which could be ascribed to a double bond. Hence it appears that the inert double bond in tumulosic acid and its dihydro-derivative is tetrasubstituted.

On oxidation by the Oppenauer method tumulosic acid gave a diketo-acid, tumulosodionic acid, indicating that the hydroxyl groups are secondary. Oxidation of methyl *O*-diacetyltumulosate with selenium dioxide yielded an intractable mixture, but with this reagent methyl *O*-diacetyldihydrotumulosate furnished a good yield of methyl *O*-diacetyldehydrodihydrotumulosate which on deacetylation gave methyl dehydrodihydrotumulosate. Methyl *O*-diacetyldehydrodihydrotumulosate showed selective absorption in the ultra-violet with a maximum at 234 mμ (log ε 4·25) and subsidiary peaks at 236 and 251 mμ (log ε 4·19, 4·08), and selective absorption in the infra-red with a peak at 817 cm.$^{-1}$, indicating the presence of the transoid heteroannular diene system (I) (cf. Voser, Montavon, Günthard, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1950, **33**, 1893, and Part XVII, *loc. cit.*). Further, it appears that this diene system has arisen from the partial structure (II) present in methyl *O*-diacetyldihydrotumulosate.

(I)   (II)

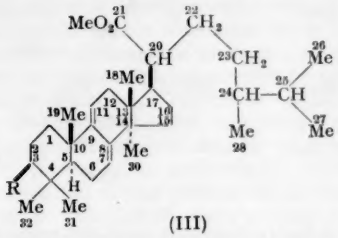
In an attempt to resolve the natural mixture of acids from *P. tumulosus* by the procedure employed for the natural mixed eburicoic and dehydroeburicoic acid (Part XVII, *loc. cit.*) the tumulosic–dehydrotumulosic acid mixture was oxidised by the Oppenauer method, but the resulting mixture of diketo-acids proved intractable. When, however, the mixture of tumulosic and dehydrotumulosic acid was successively acetylated, esterified with diazomethane, and hydrogenated, and the resulting mixture of methyl *O*-diacetyldidihydro- and *O*-diacetyldehydrodihydro-tumulosate was oxidised with selenium dioxide the homogeneous product consisted of methyl *O*-diacetyldehydrodihydrotumulosate, thus supporting the view that the component of the natural mixed acids showing absorption in the ultra-violet is dehydrotumulosic acid. On oxidation with selenium dioxide the product obtained by acetylation and subsequent hydrogenation of the mixed acids gave *O*-diacetyldehydrodihydrotumulosic acid which appeared to be homogeneous, but when this was deacetylated and the product subsequently esterified a somewhat impure methyl dehydrodihydrotumulosate was obtained which could not be readily purified by recrystallisation. Acetylation of this ester, however, gave methyl *O*-diacetyldehydrodihydrotumulosate.

In the course of experiments devised to relate tumulosic acid to compounds of known structure it was found that mild oxidation of methyl dehydrodihydrotumulosate with chromic anhydride gave methyl dehydrodihydrotumulosodionate, characterised as the bis-2 : 4-dinitrophenylhydrazone. The absorption spectrum of this diketone indicated that both keto-groups were isolated. Reduction of the diketone by the Wolff–Kishner method gave methyl dehydrodideoxydihydrotumulosate which was shown to be identical with methyl eburico-7 : 9(11)-dien-21-oate (III; R = H) derived by the oxidation of methyl 3β-hydroxyeburico-7 : 9(11)-dien-21-oate (methyl dehydrodihydroeburicoate; Part XVII, *loc. cit.*) (III; R = OH) with chromic anhydride and subsequent reduction by the Wolff–Kishner method of the resulting methyl 3-oxoeburico-7 : 9(11)-dien-21-oate (IV). This conversion of tumulosic acid into (III; R = H) serves to show that tumulosic and dehydrotumulosic acid contain the carbon skeleton of eburicoic acid and also that the relative positions of the carboxyl groups and inert double bonds are those obtaining in eburicoic and dehydroeburicoic acids respectively (Part XIX, *loc. cit.*).

The alcoholic hydroxyl groups in tumulosic acid were readily located. Comparison of methyl dehydrodihydrotumulosodionate with methyl 3 : 16-dioxoeburico-7 : 9(11)-dien-21-oate (V) derived from polyporenic acid C, now believed to be 16α-hydroxy-3-oxoeburico-

7 : 9(11) : 24(28)-trien-21-oic acid (VI) (Bowers, Halsall, and Sayer, *J.*, 1954, 3070; cf. Bowers, Halsall, Jones, and Lemin, *J.*, 1953, 2548), showed that these compounds were identical, thus proving that the two keto-groups of methyl dehydrodihydrotumulosodionate and hence the two hydroxyl groups in tumulosic acid are located at $C_{(3)}$ and $C_{(16)}$.

The stereochemical configurations of the hydroxyl groups in tumulosic acid are established by the fact that methyl dehydrodihydrotumulosate and methyl *O*-diacetyldehydrodihydrotumulosate were respectively identical with methyl 3 : 16-dihydroxyeburico-7 : 9(11)-dien-21-oate (VII; R = Me, R′ = R″ = H) and its diacetate (VII; R = Me,



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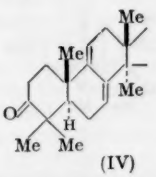
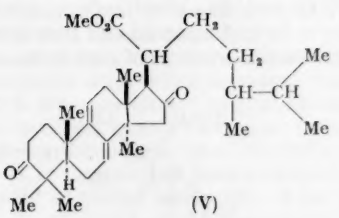
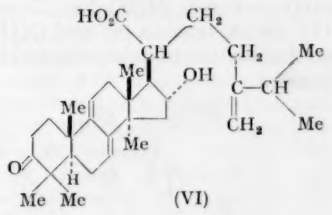


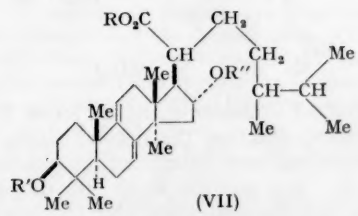
(IV)



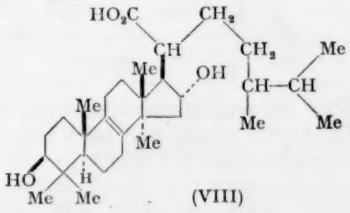
(V)



(VI)



(VII)



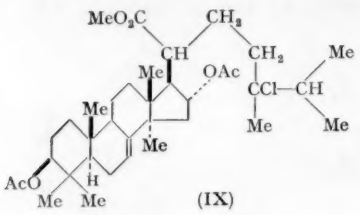
(VIII)

R′ = R″ = Ac) derived from polyporenic acid C (VI) (*idem*, *loc. cit.*). It is known that the 3-hydroxyl group in (VII) has the β(equatorial)-configuration (*idem*, *loc. cit.*) and it has recently been shown that the 16-hydroxyl group in polyporenic acid has the α-configuration (Bowers, Halsall, and Sayer, *loc. cit.*). Hence, dihydrotumulosic and dehydrodihydrotumulosic acid are, respectively, 3β : 16α-dihydroxyeburic-8-en-21-oic acid (VIII) and 3β : 16α-dihydroxyeburico-7 : 9(11)-dien-21-oic acid (VII; R = R′ = R″ = H).

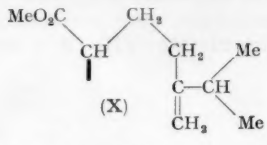
The position of the vinylidene group in tumulosic acid was established by a method analogous to that employed for eburicoic acid (Part XIX, *loc. cit.*). Treatment of methyl *O*-diacetyltumulosate with chloroformic hydrogen chloride gave an adduct containing a lablile chlorine atom. As expected by analogy with methyl 3β-acetoxyeburico-8 : 24(28)-dien-21-oate (cf. Part XIX, *loc. cit.*) this addition was accompanied by migration of the inert double bond from the Δ^8- to the Δ^7-position as shown by the presence of a peak at 817 cm.$^{-1}$ in the infra-red spectrum of the hydrochloride which is therefore formulated as (IX).

By the action of acetic anhydride on (IX), hydrogen chloride was eliminated, giving a mixture of isomeric compounds which differ only in the position of the reactive double bond and are respectively methyl 3β : 16α-diacetoxyeburico-7 : 24(28)-dien-21-oate (X)

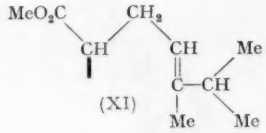
and methyl 3β : 16α-diacetoxyeburico-7 : 23-dien-21-oate (XI). The infra-red absorption spectrum of the mixture exhibited peaks at 890, 828, and 817 cm.$^{-1}$, due, respectively, to the 24 : 28-, 23 : 24-, and 7 : 8-double bonds. This diene mixture could not be separated but on ozonolysis gave formaldehyde and methyl *iso*propyl ketone (characterised as the dimethone and 2 : 4-dinitrophenylhydrazone respectively) as the sole volatile carbonyl products. This is in accordance with the formulæ postulated for the components (X)



(IX)

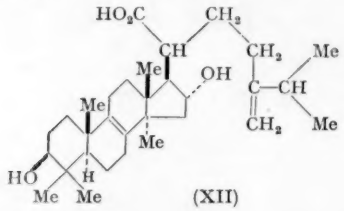


(X)

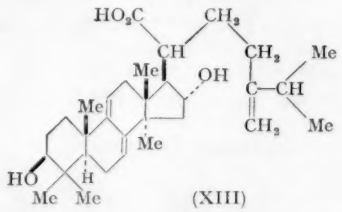


(XI)

and (XI) and hence tumulosic acid and dehydrotumulosic acid are respectively 3β : 16α-dihydroxyeburico-8 : 24(28)-dien-21-oic acid (XII) and 3β : 16α-dihydroxyeburico-7 : 9(11) : 24(28)-trien-21-oic acid (XIII). Owing to lack of material and their intractable nature, the mixture of aldehydic and ketonic non-volatile products of ozonolysis could not be separated.



(XII)



(XIII)

After the present communication had been drafted Professor E. R. H. Jones, F.R.S., of Manchester kindly sent us a copy of a communication on the natural mixed acids " Polyporenic acid B " which he and his collaborators have submitted for publication. They have shown that this " polyporenic acid B " is a mixture of 3β : 16α-dihydroxyeburico-8 : 24(28)-dien-21-oic acid (XII) and its dehydro-derivative (XIII). Since the Manchester authors have not yet isolated from the mixture pure 3β : 16α-dihydroxyeburico-8 : 24(28)-dien-21-oic acid which we had provisionally termed tumulosic acid we have at present, for convenience and brevity, retained this trivial name.

Experimental

Unless stated otherwise, optical rotations were measured in chloroform at room temperature (18—22°) with a 1-dm. tube, ultra-violet absorption spectra in 95% alcohol with a Unicam spectrophotometer, and infra-red spectra in " Nujol " pastes with a Grubb-Parsons single-beam spectrometer. The light petroleum used had b. p. 60—80°.

The fungi were cultivated on the modified Williams and Saunders medium (Part XVII, *loc. cit.*), and the dry pulverised mycelium was exhaustively extracted with light petroleum and then with ether.

Tumulosic Acid from Polyporus tumulosus *Cook and from* P. australiensis *Wakefield.*—The residue left on evaporation of the light petroleum extract from the mycelium of *P. tumulosus* Cooke was repeatedly recrystallised from aqueous alcohol, yielding ergosterol hydrate in colourless laminae, m. p. and mixed m. p. 160—162°, $[\alpha]_D$ −124° (*c*, 2·20), $\lambda_{max.}$ 262·5, 271, 281, 293·5 mμ (ε 7700, 11,100, 11,700, 6700) (Found : C, 81·3; H, 10·8. Calc. for $C_{28}H_{44}O,H_2O$:

C, 81·1; H, 11·2%). The acetate had m. p. and mixed m. p. 174—176°, $[\alpha]_D$ −91·5° (*c*, 1·12) (Found: C, 82·0; H, 10·5. Calc. for $C_{30}H_{46}O_2$: C, 82·1; H, 10·6%).

The product from the ethereal extract of the mycelium of *P. tumulosus* was digested with boiling 15% aqueous sodium carbonate, and a solution of the resulting insoluble sodium salts in boiling alcohol was diluted with 1% aqueous sodium hydroxide solution until the mixture of crystalline sodium tumulosate and dehydrotumulosate began to separate. This solid was recrystallised from methanol–ethyl acetate (1 : 1) (yield of the crude salt was about 3% of the weight of the dry mycelium).

By the same procedure the mixture of salts (yield, 2%) was isolated from *P. australiensis* Wakefield grown on the synthetic medium and from the sporophores of the naturally grown mould (yield, 2%), collected near Bateman's Bay, N.S.W., Australia.

Decomposition of the sodium salts from the mycelium of *P. tumulosus* with boiling acetic acid gave the mixture of tumulosic and dehydrotumulosic acid which separated from ethyl acetate frequently as an amorphous powder or (seldom) in rectangular plates, m. p. 318°, $[\alpha]_D$ +8·6° (*c*, 4·5 in pyridine). Treatment of the mixed sodium salts (1 g.) with excess of methyl iodide in boiling methanol (5 ml.) for 5 hr. and extraction of product with benzene gave a gum (0·8 g.) which on crystallisation from methanol furnished the mixture of methyl esters in truncated prisms, m. p. 163—164·5°, $[\alpha]_D$ +28° (*c*, 2·6) (Found: C, 76·4; H, 10·7; OMe, 6·2%). Acetylation of this yielded the mixture of the diacetates of the esters, forming slender needles, m. p. 155—156·5°, from methanol, $[\alpha]_D$ +7·0° (*c*, 2·2) (Found: C, 73·6; H, 9·4; OMe, 5·5%). The respective mixed diacetates, methyl esters, and diacetyl derivatives of the methyl esters from *P. tumulosus* and *P. australiensis* had identical infra-red absorption spectra (with 25% solutions in CS_2).

Treatment of the mixed acids or salts with hot acetic anhydride–pyridine gave a mixture of the acetylated acids which separated from aqueous alcohol in needles, m. p. 229—230°, $[\alpha]_D$ +6·4° (*c*, 8·5 in pyridine); $E^{1\%}_{1\,cm.}$ at 243 mμ varied from 73 to 110 in material from different batches of mycelium from *P. tumulosus* Cooke, and $E^{1\%}_{1\,cm.}$ 37 at 243 mμ from the mycelium of *P. australiensis* (Found: C, 73·5; H, 9·7%). A solution of this mixture (43·2 g.) from the mycelium of *P. tumulosus* in light petroleum–benzene (3·2 l.; 4 : 1) was poured on a column of neutralised aluminium oxide (60 × 6 cm.) which was eluted with light petroleum–benzene (16·5 l., 4 : 1; then 18 l., 1 : 1), benzene (5 l.), acetone–benzene (21·5 l., 1 : 19; 16·5 l., 1 : 9; 5·3 l., 1 : 4), and finally methanol (2 l.), giving fractions in which $E^{1\%}_{1\,cm.}$ at 243 mμ progressively increased from 6·5 to 175. The fractions of lower intensity were repeatedly rechromatographed, ultimately giving *O-diacetyltumulosic acid* (3·2 g.) which did not show selective absorption in the near ultra-violet and appeared to be dimorphic, separating from dilute alcohol as a mixture of plates and rods, m. p. 217—228° (mechanically separated, the rods had m. p. 214°), and from aqueous acetone in plates, m. p. 228° with sintering at 214°, $[\alpha]_D$ +6·7° (*c*, 2·01) [Found: C, 73·4; H, 9·4; OAc, 20·1, 20·4%; *M* (Rast), 551, 576, 561. $C_{31}H_{48}O_2(OAc)_2$ requires C, 73·6; H, 9·5; OAc, 20·7%; *M*, 571].

O-Diacetyltumulosic acid (210 mg.) was boiled with 5% alcoholic potassium hydroxide (8 ml.) for 1 hr. and the solution diluted with water (20 ml.), concentrated (to 18 ml.), and cooled, giving potassium tumulosate in fine needles. On being cooled, a solution of the dried salt in the minimum amount of boiling acetic acid (*ca.* 10 ml.) deposited amorphous *tumulosic acid* (116 mg.) which was dissolved in boiling aqueous alcohol. When this was concentrated the boiling solution deposited the acid in small needles, m. p. 306° (decomp.), $[\alpha]_D$ +8·1° (*c*, 3·30 in pyridine) (Found: C, 76·3; H, 10·2. $C_{31}H_{50}O_4$ requires C, 76·5; H, 10·4%). Tumulosic acid, which sublimed unchanged in a high vacuum and gave a bright purple-red colour in the Liebermann–Burchard reaction, was insoluble in benzene or light petroleum, very slightly soluble in chloroform, and more soluble in alcohol, methanol, or pyridine. The sodium and potassium salts were readily soluble in alcohol and insoluble in water.

The action of warm methyl iodide on sodium tumulosate or of ethereal diazomethane on tumulosic acid gave *methyl tumulosate*, forming rosettes of colourless needles, m. p. 164—164·5°, $[\alpha]_D$ +26·6° (*c*, 1·69), from methanol (Found: C, 76·6; H, 10·4; OMe, 6·6. $C_{32}H_{52}O_4$ requires C, 76·8; H, 10·5; OMe, 6·2%). Prepared by the acetic anhydride–pyridine method, *methyl O-diacetyltumulosate* separated from methanol in colourless needles, m. p. 159—159·5°, $[\alpha]_D$ +6·5° (*c*, 0·70), identical with a specimen formed by the action of ethereal diazomethane on *O*-diacetyltumulosic acid (Found: C, 73·7; H, 9·4: OMe, 5·3. $C_{36}H_{56}O_6$ requires C, 73·9; H, 9·7; OMe, 5·3%).

O-Diacetyldihydrotumulosic Acid.—Hydrogenation of *O*-diacetyltumulosic acid (1 g.) in alcohol (100 ml.) with hydrogen (approx. 1·07 mol. absorbed) at atmospheric temperature and

pressure and a palladium–charcoal catalyst was complete in ½ hr., giving O-*diacetyldihydrotumulosic acid*, which separated from aqueous alcohol in needles (0·8 g.), m. p. 231—231·5°, $[\alpha]_D$ +1·5° (*c*, 0·77), with a yellow tetranitromethane reaction in chloroform (Found: C, 73·3; H, 9·6. $C_{35}H_{56}O_6$ requires C, 73·4; H, 9·9%). The use of Adams catalyst in acetic acid gave the same dihydro-derivative.

Hydrogenation of methyl *O*-diacetyltumulosate with Adams catalyst and hydrogen (1 mol. absorbed) in acetic acid yielded *methyl O-diacetyldihydrotumulosate* which separated from aqueous methanol in needles, m. p. 183—184°, $[\alpha]_D$ +1·4° (*c*, 8·4), giving a yellow colour with tetranitromethane in chloroform (Found: C, 73·4; H, 9·8; OMe, 5·3. $C_{36}H_{58}O_6$ requires C, 73·7; H, 10·0; OMe, 5·3%).

Oxidation of Methyl O-*Diacetyltumulosate with Osmium Tetroxide.*—Osmium tetroxide (0·5 g.) was added to a solution of the ester (1·35 g.) in ether (20 ml.), the mixture kept at room temperature for 6 days, and the solvent evaporated. A solution of the black residue in methanol (20 ml.) was added to sodium sulphite (10 g.), dissolved in water (80 ml.), and the mixture heated under reflux for 1 hr., cooled, and filtered. Extraction of the solid with boiling methanol (15 ml. × 5) gave the *diol* in small needles (105 mg.) which on recrystallisation from the same solvent had m. p. 198—199° (Found: C, 69·8; H, 9·7; OMe, 5·0. $C_{36}H_{58}O_8$ requires C, 69·9; H, 9·5; OMe, 5·0%).

A solution of the diol (317 mg.) and lead tetra-acetate (180 mg.) in acetic acid (5 ml.) was kept at room temperature for ½ hour and poured into water, giving a gel. The volatile products were removed with steam, leaving a precipitate which did not crystallise, formed an amorphous semicarbazone and 2 : 4-dinitrophenylhydrazone, and did not react with sodium hypoiodite. The distillate contained formaldehyde which was isolated as the 2 : 4-dinitrophenylhydrazone (75 mg., 0·70 mol.), m. p. and mixed m. p. 164° (Found: C, 40·2; H, 3·0; N, 26·3. Calc. for $C_7H_6O_4N_4$: C, 40·0; H, 2·9; N, 26·7%). In another experiment the formaldehyde was converted into the dimedone derivative, m. p. and mixed m. p. 187° (Found: C, 69·5; H, 8·5. Calc. for $C_{17}H_{24}O_4$: C, 69·8; 8·3%).

Tumulosodionic Acid [3 : 16-*Dioxoeburico*-8 : 24(28)-*dien*-21-*oic Acid*].—A mixture of tumulosic acid (0·77 g.), aluminium *tert.*-butoxide (1·5 g.), *cyclo*hexanone (1·8 ml.), and dioxan (6·5 ml.) was heated under reflux for 11 hr. cooled, and diluted with an excess of 2N-sulphuric acid. The dioxan and excess of *cyclo*hexanone were removed with steam, and the residual solid was extracted with hot 1% aqueous sodium hydroxide (100 ml.). The filtered extract was concentrated (to 35 ml.) and treated with sodium carbonate (3·5 g.), giving sodium tumulosodionate which on isolation was dissolved in hot water (40 ml.) and decomposed with hydrochloric acid. The resulting *tumulosodionic acid* (0·185 g.) separated from aqueous alcohol as a colourless microcrystalline solid, m. p. 280—281° (decomp.), $\lambda_{max.}$ 285 mμ (log ε 1·87) (Found: C, 77·5; H, 9·8. $C_{31}H_{46}O_4$ requires C, 77·1; H, 9·6%).

Oxidation of mixed tumulosic and dehydrotumulosic acid under the same conditions gave a product which did not crystallise.

Methyl O-*Diacetyldehydrodihydrotumulosate* (*Methyl* 3β : 16α-*Diacetoxyeburico*-7 : 9(11)-*dien*-21-*oate*) (VII; R = Me, R′ = R″ = Ac).—A mixture of methyl *O*-diacetyldihydrotumulosate (methyl 3β : 16α-diacetoxyeburic-8-en-21-oate) (0·5 g.), selenium dioxide (1·3 g.), acetic acid (14 ml.), and water (1 ml.) was heated under reflux for 12 hr., filtered, and diluted with water (200 ml.). After crystallisation from methanol, the resulting product (0·28 g.) was purified by chromatography from benzene on aluminium oxide, followed by crystallisation from methanol, forming colourless needles, m. p. 170—170·5°, undepressed on admixture with methyl 3β : 16α-diacetoxyeburico-7 : 9(11)-dien-21-oate prepared from polyporenic acid C (Bowers, Halsall, Jones, and Lemin, *loc. cit.*); the product had $[\alpha]_D$ +21° (*c*, 1·18), $\lambda_{max.}$ 236, 243, 251 mμ (log ε 4·19, 4·25, 4·08) (Found: C, 74·0; H, 9·5; OMe, 5·2. Calc. for $C_{36}H_{56}O_6$: C, 73·9; H, 9·7; OMe, 5·3%). The infra-red spectrum was identical with that of a sample of methyl 3β : 16α-diacetoxyeburico-7 : 9(11)-dien-21-oate.

Under the same conditions the oxidation of a mixture of methyl *O*-diacetyldihydrotumulosate and methyl *O*-diacetyldehydrodihydrotumulosate (0·5 g.), prepared from the acidic complex isolated from the mycelium of *P. tumulosus*, gave methyl *O*-diacetyldehydrodihydrotumulosate (0·25 g.), m. p. and mixed m. p. 170—171°, $[\alpha]_D$ +22° (*c*, 2·09), having an infra-red spectrum identical with that of a sample of authentic material, measured with 25% solutions in CS_2.

O-*Diacetyldehydrodihydrotumulosic Acid* [3β : 16α-*Diacetoxyeburico*-7 : 9(11)-*dien*-21-*oic Acid*) (VII: R = H, R′ = R″ = Ac].—The acidic mixture from the mycelium was hydrogenated with the aid of Adams catalyst, and the product acetylated. The resulting mixture of dihydrodiacetates (80 g.) was oxidised with selenium dioxide by the procedure described above and a

solution of the crude product in benzene (4 l.) poured on to neutralised aluminium oxide (80 cm. × 6 cm.). Eluted with benzene followed by acetone–benzene (1 : 19), the compound (33·6 g.) was contaminated with selenium. A mixture of this material (2·1 g.), potassium hydroxide (4 g.), and alcohol (80 ml.) was heated under reflux for 1 hr., diluted with water (200 ml.), and concentrated (to 180 ml.). Potassium dehydrodihydrotumulosate then separated in fine needles and was decomposed with boiling acetic acid (100 ml.), giving *dehydrodihydrotumulosic acid* (VII; R = R′ = R″ = H) (1·4 g.) which separated from aqueous alcohol in short colourless needles, m. p. 324° (decomp.), $[\alpha]_D$ +26° (*c*, 2·1 in EtOH; 4-dm. tube), $\lambda_{max.}$ 236, 243, and 251 mμ (log ε 4·17, 4·24, 4·04) (Found: C, 76·2; H, 10·3. $C_{31}H_{50}O_4$ requires C, 76·5; H, 10·4%). By the pyridine–acetic anhydride method, this acid gave the *diacetyl* derivative which formed colourless needles, m. p. 231°, from alcohol, $[\alpha]_D$ +21·5° (*c*, 2·18), $\lambda_{max.}$ 236, 243, and 251 mμ (log ε 4·19, 4·24, 4·07) (Found: C, 73·2; H, 9·7. $C_{35}H_{54}O_6$ requires C, 73·6; H, 9·5%).

Methyl Dehydrodihydrotumulosate [*Methyl* 3β : 16α-*Dihydroxyeburico*-7 : 9(11)-*dien*-21-*oate*] (VII; R = Me, R′ = R″ = H).—(*A*) A solution of methyl *O*-diacetyldehydrodihydrotumulosate (11 g.) in methanol (600 ml.), containing potassium hydroxide (60 g.), was heated under reflux for 50 min., cooled, and poured into water (1·5 l.). Isolated with ether, the resulting methyl dehydrodihydrotumulosate (5·9 g.) separated from aqueous methanol in colourless needles, m. p. 184·5—185·5°, $[\alpha]_D$ +27° (*c*, 2·08), $\lambda_{max.}$ 236, 243, and 251 mμ (log ε 4·17, 4·24, 4·07) (Found: C, 76·7; H, 10·7; OMe, 6·4. Calc. for $C_{32}H_{52}O_4$: C, 76·7; H, 10·5; OMe, 6·2%). On being kept, the aqueous liquor deposited a further quantity of material which was collected 3 days later and on treatment with ethereal diazomethane gave more methyl ester (1·9 g.), m. p. 183—185°. Thus obtained, methyl dehydrodihydrotumulosate was identical with methyl 3β : 16α-dihydroxyeburico-7 : 9(11)-dien-21-oate (m. p. 185—187°, $[\alpha]_D$ +27°), prepared from polyporenic acid C (Bowers, Halsall, Jones, and Lemin, *loc. cit.*) (mixed m. p. and infra-red spectrum).

(*B*) Dehydrodihydrotumulosic acid (1 g.) was esterified with ethereal diazomethane, to give methyl dehydrodihydrotumulosate (0·85 g.), m. p. 167—168°, $[\alpha]_D$ +33° (*c*, 2·50), which on repeated crystallisation from methanol had m. p. 179° (with sintering at 168°), $[\alpha]_D$ +27° (*c*, 0·82), $\lambda_{max.}$ 236, 243, and 251 mμ (log ε 4·17, 4·24, 4·07). Mixed with authentic methyl dehydrodihydrotumulosate, this had m. p. 179—184°. With acetic anhydride–pyridine the methyl ester, m. p. 167—168°, gave methyl *O*-diacetyldehydrodihydrotumulosate, m. p. and mixed m. p. 170°.

Methyl Dehydrodihydrotumulosodionate [*Methyl* 3 : 16-*Dioxoeburico*-7 : 9(11)-*dien*-21-*oate*] (V).—A solution of chromic anhydride (0·46 g.) in acetic acid (14 ml.) was added dropwise to methyl dehydrodihydrotumulosate (1·5 g.) in acetic acid (42·5 ml.) at 60° during 1 hr. and after being kept at 60° for 1 hr. the mixture was treated with a little methanol to destroy unchanged anhydride, and diluted with water (375 ml.) and saturated aqueous sodium carbonate (*ca.* 30 ml.). A solution of the dried precipitate in light petroleum–benzene (30 ml.; 1 : 1) was poured on aluminium oxide (20 × 1·2 cm.). Elution with the same solvent mixture gave methyl dehydrodihydrotumulosodionate (0·5 g.) which separated from methanol in colourless needles or from acetone in plates, m. p. 169—169·5°, $[\alpha]_D$ −67° (*c*, 0·98; 0·5-dm. micro-tube), $\lambda_{max.}$ 236, 243, 251, and 295 mμ (log ε 4·18, 4·24, 4·07, 1·86) (Found: C, 77·1; H, 9·5; OMe, 6·4. Calc. for $C_{32}H_{48}O_4$: C, 77·4; H, 9·7; OMe, 6·3%). Thus obtained, this diketo-ester was identical with a specimen of methyl 3 : 16-dioxoeburico-7 : 9(11)-dien-21-oate m. p. 166·5—168·5°, $[\alpha]_D$ −68°, prepared from polyporenic acid C (Bowers, Halsall, Jones, and Lemin, *loc. cit.*) (mixed m. p. and infra-red spectra).

The *bis*-2 : 4-*dinitrophenylhydrazone* separated from aqueous dioxan in orange aggregates, m. p. 264—266° (decomp.) (Found: C, 62·3; H, 6·9; N, 12·7; OMe, 3·6. $C_{44}H_{56}O_{10}N_8$ requires C, 61·7; H, 6·6; N, 13·1; OMe, 3·6%).

Methyl Dehydrodideoxydihydrotumulosate [*Methyl Eburico*-7 : 9(11)-*dien*-21-*oate*] (III; R = H).—(*A*) A mixture of methyl dehydrodihydrotumulosodionate (0·3 g.), potassium hydroxide (0·3 g.), 90% hydrazine hydrate (0·5 ml.), and diethylene glycol (5 ml.) was heated under reflux for 2 hr. and then at 195° for 4 hr., cooled, and poured into water (100 ml.). The washed, dried precipitate was treated with ethereal diazomethane, and the product purified by chromatography from light petroleum–benzene (1 : 1) on a small column of aluminium oxide and then by crystallisation from aqueous methanol, giving *methyl dehydrodideoxydihydrotumulosate* in colourless plates, m. p. 134°, $[\alpha]_D$ +45° (*c*, 0·91; 0·5-dm. micro-tube), $\lambda_{max.}$ 236, 243, and 251 mμ (log ε 4·17, 4·25, 4·07) (Found: C, 81·8; H, 11·2; OMe, 6·5. $C_{32}H_{52}O_2$ requires C, 82·0; H, 11·2; OMe, 6·6%).

(*B*) Methyl *O*-acetyldihydroeburicoate (methyl 3β-acetoxyeburic-8-en-21-oate) (from eburicoic acid; Part XVI, *loc. cit.*) was oxidised with selenium dioxide under the usual conditions, giving methyl *O*-acetyldehydrodihydroeburicoate [methyl 3β-acetoxyeburico-7 : 9(11)-dien-21-oate] (Part XVII, *loc. cit.*) which, on hydrolysis with hot 5% methanolic potassium hydroxide, furnished methyl dehydrodihydroeburicoate [methyl 3β-hydroxyeburico-7 : 9(11)-dien-21-oate] (Part XVII, *loc cit.*) subsequently oxidised with chromic anhydride under the usual conditions to methyl dehydrodihydroeburiconate [methyl 3-oxoeburico-7 : 9(11)-dien-21-oate; Part XVII, *loc. cit.*].

Reduction of this compound (0·77 g.) by the Wolff–Kishner procedure described above gave methyl eburico-7 : 9(11)-dien-21-oate (0·22 g.) which separated from methanol in colourless plates, m. p. 134°, $[\alpha]_D$ +46° (*c*, 1·0; 0·5-dm. micro-tube), $\lambda_{max.}$ 236, 243, and 251 mμ (log ε 4·17, 4·25, 4·07) (Found: C, 81·9; H, 11·2; OMe, 6·6%), and was identical with methyl dehydrodideoxydihydrotumulosate (mixed m. p. and infra-red spectra).

Isomerisation of Methyl O-*Diacetyltumulosate.*—A stream of hydrogen chloride was led into a solution of this ester (1·3 g.) in chloroform (15 ml.) at room temperature for 7 hr., and next day the solvent was distilled in a vacuum and a solution of the residue in light petroleum (25 ml.) was poured on aluminium oxide (10 × 1·2 cm.). Eluted with the same solvent, the *hydrochloride* formed colourless needles (0·5 g.), m. p. 164—166°, from methanol, $[\alpha]_D$ +3·8° (*c*, 2·69) (Found: C, 69·0; H, 9·4; Cl, 5·2; OMe, 5·3. $C_{36}H_{56}O_6$,HCl requires C, 69·6; H, 9·3; Cl, 5·7; OMe, 5·0%). A solution of this hydrochloride (0·5 g.) in acetic anhydride (6·5 ml.) was boiled for 10 hr., diluted with water (65 ml.), and kept for 16 hr. Repeated crystallisation of the resulting precipitate from methanol gave a mixture of methyl 3β : 16α-diacetoxyeburico-7 : 23-dien-21-oate and methyl 3β : 16α-diacetoxyeburico-7 : 24(28)-dien-21-oate, m. p. 179—180° (Found: C, 73·7; H, 9·9; OMe, 5·4. Calc. for $C_{36}H_{56}O_6$: C, 73·9; H, 9·7; OMe, 5·3%).

Ozonolysis of this mixture (1·6 g.) in acetic acid (50 ml.), followed by removal of the volatile products with steam, gave a distillate which on treatment with ½% aqueous dimedone (200 ml.) furnished the formaldehyde derivative (0·15 g.), m. p. and mixed m. p. 187°, of dimedone. Distillation of the aqueous filtrate from the dimedone reaction mixture and treatment of this distillate with 1% aqueous 2 : 4-dinitrophenylhydrazine sulphate (80 ml.) yielded the 2 : 4-dinitrophenylhydrazone (0·46 g.) of methyl *iso*propyl ketone which was purified by chromatography on neutralised aluminium oxide and then from methanol, forming orange prisms, m. p. 120°, identical with an authentic specimen (Found: C, 49·3; H, 5·2; N, 21·1. Calc. for $C_{11}H_{14}O_4N_4$: C, 49·6; H, 5·3; N, 21·0%). No other volatile carbonyl compound was detected.

Appendix

In continuation of studies on the metabolic products of Basidiomycete fungi the mycelial products from strains of *Poria cocos* (Schw.) Wolf (syn. *Pachyma Hoelen* Rumph.) grown artificially have been examined. From the naturally occurring sclerotium of this species Nakanisi, Yamamoto, and Ikeda (*J. Pharm. Soc. Japan*, 1939, **59**, 725) isolated a hydroxy-lactonic acid, $C_{30}H_{44}O_5$, named pachymic acid. Through the kindness of Dr. R. W. Davidson, Division of Forest Pathology, United States Department of Agriculture, seven strains of this species were obtained, *viz.*, Nos. 71693, 71692-R, 71730-S, 72152, 90852-R, 90886-T, and 94401, and have been grown on the artificial medium. The mycelium from strains 71693, 71692-R, and 90852-R contained the mixture of eburicoic and dehydroeburicoic acid (Part XVII, *loc. cit.*), strain No. 94401 furnished the mixture of tumulosic and dehydrotumulosic acid, whilst the mycelium of the remaining three species gave quantities of material insufficient for examination. Pachymic acid did not appear to be produced by the strains thus examined.

Eburicoic acid was obtained from the mycelium of *Polyporus hispidus* accompanied by only a trace of dehydroeburicoic acid.

Experimental

Eburicoic and Tumulosic Acid from Strains of Poria cocos, *Wolf.*—The light petroleum extract of the mycelium from the seven strains supplied by Dr. R. W. Davidson showed selective ultra-violet absorption with peaks at 260, 271, 281, and 295 mμ, indicating the presence of ergosterol or an ergosterol-like substance. On extraction with ether the mycelium from No. 71693 gave a mixture of eburicoic and dehydroeburicoic acid, m. p. and mixed m. p. 281—283°,

$[\alpha]_D$ +44° (*c*, 0·12; 4 dm. tube), $\lambda_{max.}$ 235, 243, and 251 mμ ($E^{1\%}_{1cm.}$ 100, 116, and 77 respectively) (Found: C, 79·1; H, 10·6. Calc. for $C_{31}H_{50}O_3$: C, 79·1; H, 10·7. Calc. for $C_{31}H_{48}O_3$: C, 79·4; H, 10·3%) (cf. Part XVII, *loc. cit.*). The acetyl derivative of this mixture had m. p. and mixed m. p. 251—253°, $[\alpha]_D$ +53° (*c*, 1·1) (Found: C, 77·6; H, 10·0. Calc. for $C_{33}H_{52}O_4$: C, 77·3; H, 10·2. Calc. for $C_{33}H_{50}O_4$: C, 77·6; H, 9·9%). The mixture of the same acids from No. 71692-R had m. p. and mixed m. p. 282—283°, $[\alpha]_D$ +43° (*c*, 0·09; 4-dm. tube), $\lambda_{max.}$ 235, 243, and 252 mμ ($E^{1\%}_{1cm.}$ 194, 229, and 153 respectively) (Found: C, 78·9; H, 10·5%), giving an acetyl derivative, m. p. and mixed m. p. 250—251°, $[\alpha]_D$ +60·5° (*c*, 2·02) (Found: C, 77·2; H, 9·9%), and from No. 90852-R had m. p. and mixed m. p. 283—285°, $[\alpha]_D$ +38° (*c*, 0·27; 4-dm. tube), $\lambda_{max.}$ 234, 243, and 252 mμ ($E^{1\%}_{1cm.}$ 123, 143, and 99 respectively), giving an acetyl derivative, m. p. and mixed m. p. 248—250°, $[\alpha]_D$ +58·5° (*c*, 0·6) (Found: C, 77·5; H, 9·9%). The acetyl derivatives of the acid mixtures isolated from the 3 strains had infra-red spectra identical with that of an authentic mixture of *O*-acetyleburicoic and *O*-acetyldehydroeburicoic acid (3 : 1).

From strain No. 94401 a mixture of tumulosic and dehydrotumulosic acid was isolated, having m. p. and mixed m. p. 308—310° (decomp.) (Found: C, 76·1; H, 10·1%), which gave the *O*-diacetyl derivative, m. p. and mixed m. p. 224—227°, $[\alpha]_D$ +7·5° (*c*, 2·01), $\lambda_{max.}$ 236, 243, and 252 mμ ($E^{1\%}_{1cm.}$ 83, 86, and 57 respectively) (Found: C, 73·4; H, 9·6%); the mixed methyl ester had m. p. and mixed m. p. 166—167°, $[\alpha]_D$ +26° (*c*, 2·01) (Found: C, 76·2; H, 10·3%), and the diacetate of the mixed methyl ester, m. p. and mixed m. p. 156—158°, $[\alpha]_D$ +9·6° (*c*, 1·83) (Found: C, 73·7; H, 9·8%). The infra-red spectrum of the acetyl derivative was identical with that of acetylated tumulosic–dehydrotumulosic acid from *P. tumulosus*.

Eburicoic Acid from P. hispidus *Bull* (*Fr.*).—After the removal of the ergosterol fraction from the mycelium with light petroleum, extraction with ether gave a pale brown, crystalline product which on recrystallisation from methanol, alcohol, and finally methanol–benzene (19 : 1) furnished eburicoic acid in colourless needles, m. p. and mixed m. p. 288—290° (decomp.), $[\alpha]_D$ +48° (*c*, 2·0; chloroform–alcohol, 4 : 1), showing very weak selective absorption in the ultra-violet at 243 mμ ($E^{1\%}_{1cm.}$ 2·3) with subsidiary peaks at 236 and 251 mμ (Found: C, 78·9; H, 10·7. Calc. for $C_{31}H_{50}O_3$: C, 79·1; H, 10·7%). Methyl eburicoate had m. p. and mixed m. p. 140—141°, $[\alpha]_D$ +47° (*c*, 0·57) (Found: C, 79·1; H, 10·7; OMe, 6·2. Calc. for $C_{32}H_{52}O_3$: C, 79·3; H, 10·9; OMe, 6·4%); *O*-acetyleburicoic acid had m. p. and mixed m. p. 255—257°, $[\alpha]_D$ +47° (*c*, 2·0) (Found: C, 77·3; H, 10·2. Calc. for $C_{33}H_{52}O_4$: C, 77·3; H, 10·2%), and methyl *O*-acetyleburicoate m. p. and mixed m. p. 153—155°, $[\alpha]_D$ +47° (*c*, 1·19) (Found: C, 77·5; H, 10·5; OMe, 6·0. Calc. for $C_{34}H_{54}O_4$: C, 77·5; H, 10·3; OMe, 5·9%); the infra-red absorption spectra of these derivatives were identical with those of authentic specimens (Part XVI, *loc. cit.*).

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1 : 2-*Dicarboxylic Acids. Part II.* The Diastereoisomeric αα′-Dimethylsuccinic Acids and their Derivatives. Effect of Conformation on Stability.*

By R. P. Linstead and Margaret Whalley.

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The relative stabilities of the two diastereoisomeric αα′-dimethylsuccinic acids and of their open-chain and heterocyclic derivatives are reviewed. The results are the exact opposite of those encountered among the corresponding hexahydrophthalic acids and their derivatives. This difference is explained in terms of conformations.

The preparative methods for the αα′-dimethylsuccinic acids and their derivatives are compared and the literature is corrected in certain respects. The two diastereoisomeric nitriles have been made.

We were first led to study the αα′-dimethylsuccinic acids from interest in the synthesis of dimethylsuccinimidine and octamethyltetrazaporphin. This required, in particular, a reinvestigation of the nitrogenous derivatives such as the imides. However, a wider interest was involved. The acids constitute a classical example of stereoisomerism involving two adjacent asymmetric carbon atoms; after the tartaric acids, they are perhaps the best investigated system of the kind. Inversions between the two stereoisomeric series (*DL* † and *meso*) can be studied at various points and thus a direct indication can be obtained of the relative stabilities of the various forms. We find that the results are capable of an orderly explanation on the basis of conformations.

It is generally accepted that the most stable conformation of the ethane molecule is staggered; similarly the preferred arrangement of *n*-butane, with the lowest potential energy, is one in which the four carbon atoms lie in a planar zig-zag. If hydrogen atoms in the 2- and the 3-position in butane are substituted, structural factors are introduced which affect the stability of the simple zig-zag type with results that can be studied chemically. As will appear in the sequel, the αα′-dimethylsuccinic acids are very convenient compounds for this purpose.

The Diastereoisomeric αα′-Dimethylsuccinic Acids.—We first examined the preparation of ten key crystalline compounds: the parent acids, and the amides, nitriles, anhydrides, and imides of the two series. Our data on the acids, anhydrides, and the *DL*-imides agreed substantially with those in the literature, but in earlier work on the two amides and the *meso*-imide the pure isomerides were not obtained owing to the ease of inversion. The two dinitriles (2 : 3-dicyanobutanes) are new (see Table 1).

The methods for the preparation of the acids are described in a later section. They yielded mixtures of isomerides, generally in about equal amounts. The *meso*-acid, m. p. 209°, was easily separated by crystallisation. On esterification with methanol and mineral acid in boiling benzene it gave a pure *meso*-ester. (The configuration of this and of the other derivatives described later was determined by hydrolysis with boiling hydrochloric acid for two hours. Separate experiments showed that the *meso*-acid was completely unaffected by this treatment and the *DL*-acid almost so. The *DL*-acid was gradually isomerised by long treatment under these conditions so that *prolonged* acid hydrolysis of *DL*-derivatives does not give reliable evidence of configuration, particularly as the less soluble *meso*-acid tends to crystallise first from hydrolysates.) The *meso*-ester failed to give a diamide with aqueous or methanolic ammonia at room temperature or with methanolic ammonia at 90°. At 165° with aqueous-methanolic ammonia, however, it slowly yielded the pure *meso*-diamide, m. p. 301—303°. This diamide could not be obtained from the *DL*-imide on treatment with ammonia under a variety of conditions. Dehydration of the *meso*-amide with carbonyl chloride in pyridine gave the *meso*-dinitrile, m. p. 45—46°. Hydrolysis of both amide and nitrile gave pure *meso*-acid. We found

* Part I, *J.*, 1953, 3490. † For use of *DL*, see *J.*, 1950, 3333, 3701, and *J.*, 1951, 3516.

the *meso*-anhydride very difficult to obtain pure. Previous workers had obtained it by the action of acetyl chloride on the *meso*-acid (Hückel and Müller, *Ber.*, 1931, **64**, 1983; Berner and Leonardsen, *Tidsskr. Kjemi*, 1943, **3**, 64). In our hands this gave essentially the *DL*-isomeride, m. p. 88—89°. However, the action of thionyl chloride on the sodium salt of the *meso*-acid yielded the *meso*-anhydride, m. p. 39—40°. Dimethylmaleic anhydride resisted catalytic hydrogenation; like other similar maleic anhydrides it appears to be a powerful poison for the usual catalysts. *meso*-1 : 2-Dimethylsuccinimide could not be prepared by conventional routes from dimethylsuccinic derivatives as these gave mixtures containing largely the *DL*-isomeride. The *meso*-imide was, however, readily obtained by catalytic hydrogenation of dimethylmaleinimide. The product melted at 45—47° and yielded the *meso*-acid on hydrolysis. The m. p. of the imide was depressed on admixture with the *DL*-isomeride. Crystallisation or sublimation led to very considerable inversion. Earlier workers have reported *meso*-imides with higher melting points (Bischoff and Voit, *Ber.*, 1889, **22**, 389; 1890, **23**, 623, m. p. 78°; Hückel and Müller, *loc. cit.*, m. p. 66—72°). We have obtained samples of imide melting in about this range, but these all contained considerable amounts of the *DL*-form. From a mixed melting point curve we estimate the Bischoff and the Hückel product to have contained about 87% and 76% respectively of the *DL*-isomeride.

The easy catalytic hydrogenation of the dimethylmaleinimide in comparison with the obstinate resistance of the corresponding anhydride is very striking. These and similar hydrogenations are being investigated further. For the present it need only be observed that the reaction of the imide provides another example of the formation of a hydride in its unstable form by one-sided addition of hydrogen (see Linstead, Doering, *et al.*, *J. Amer. Chem. Soc.*, 1942, **64**, 1985).

For the preparation of stereochemically homogeneous derivatives of the other diastereoisomeric series it was unnecessary to start with the pure *DL*-acid. The usual synthetic mixture of *DL*- and *meso*-acids was converted into the ammonium salts, dry distillation of which gave pure *DL*-imide, m. p. 107—109° (cf. Zelinsky and Krapivin, *Ber.*, 1889, **22**, 646; McRae, Weston, and Hubbs, *Canad. J. Res.*, 1937, **15**, 436). Short acid-hydrolysis of this gave nearly pure *DL*-acid, which could easily be purified by crystallisation. This process provides a reliable method for the preparation of this isomeride. Treatment of the *DL*-imide with concentrated aqueous ammonia at room temperature or with methanolic ammonia at 90° readily gave the homogeneous *DL*-diamide, m. p. 221—223°. When this compound was heated with aqueous ammonia or glacial acetic acid, as in crystallisation procedures, the melting point was raised but the product was less pure for, on hydrolysis, it gave appreciable amounts of *meso*-acid. Dehydration of the *DL*-amide by carbonyl chloride in pyridine gave in excellent yield *DL*-αα′-dimethylsuccinonitrile (2 : 3-dicyanobutane), m. p. 57—59°, which gave the *DL*-acid on hydrolysis.

Esterification of the original mixture of *meso*- and *DL*-acids gave a mixture of methyl esters which on treatment with aqueous ammonia gave, slowly and in poor yield, a mixture of diamides. The melting point of this varied in different preparations from 235° to 250°, and it was presumable mainly the *DL*-isomeride. Morrell (*J.*, 1914, **105**, 2698) reports the preparation, in poor yield, of diamides from the *meso*- and *DL*-esters and aqueous ammonia, the melting points being given as 244° "*cis*" (*meso*), and 238° "*trans*" (*DL*). McRae, Weston, and Hubbs (*loc. cit.*) obtained a diamide, m. p. 244° after crystallisation, both from the *DL*-imide and from an ester of unstated configuration. No hydrolyses are reported by these workers and there is little doubt that these various products were mixtures, containing mainly the *DL*-form.

The melting points of the various members of the two stereoisomeric series are summarised in Table 1.

At this stage reference should be made to the nomenclature of the acids. Some confusion exists in the literature owing to the superficial resemblance between the stable, high-melting, dimethylsuccinic acid (the *meso*-acid) and fumaric acid. This has led to the former being called "fumaroid" (see Beilstein's "Handbuch") and "*trans*" (see Heilbron's "Dictionary"), the labile acid of m. p. 127° (the *DL*-acid) being called

" maleinoid " or " *cis*." If, however, one considers the geometry of the heterocyclic derivatives of the *DL*-acid, then the two methyl groups are on opposite sides of the hetero-ring. This would entitle them to be called *trans*- although on the old nomenclature they belong to the " *cis* " or " maleinoid " series. Clearly the use of the terms *cis*, *trans*, maleinoid, and fumaroid is most undesirable and only the terms " *meso* " and *DL*- should be applied to these and similar compounds. The configurations have, of course, been established with certainty; they rest on the classical resolution of the *DL*-acid by Werner. An example of the confusion which may result from the use of other terms is

TABLE 1. *Melting points of αα'-dimethylsuccinic acids and their derivatives.*

	meso-Series		*DL*-Series	
	Present work	Lit.	Present work	Lit.
Acid	209°	209° [1]	127°	129° [1]
Diamide	301—303	244 [2]	221—223	238 [2]
Dinitrile	45—46	—	57—59	—
Anhydride	39—40	42—43 [1, 3, 4]	89	87,[4] 88—89 [5]
Imide	45—47	78,[4] 66—72 [6]	107—109	109—110 [7]

[1] Bone and Perkin, *J.*, 1896, **69**, 253. [2] Morrell, *loc. cit.* [3] Higson and Thorpe, *J.*, 1906, **89**, 1455. [4] Bischoff and Voit, *loc. cit.* [5] Fieser and Daudt, *J. Amer. Chem. Soc.*, 1941, **63**, 782. There is an accidental error in this paper, which refers to the high-melting acid as *DL*, the low melting as *meso*. The configurations given to the anhydrides are, however, correct. [6] Hückel and Müller, *loc. cit.* [7] Zelinsky and Krapivin, *loc. cit.*

to be seen in the paper of Kühn and Ebel (*Ber.*, 1925, **58**, 2091) where some of Auwers's early data (*Annalen*, 1899, **309**, 316) are reinterpreted. The two series are wrongly named: for example, Auwers's " *mal*-imide " (formed from both stereoisomeric amic acids by the action of acetyl chloride) becomes " *ms*-imide " in Kühn's paper. It is, in fact, the *DL*-imide (cf. Hückel and Müller, *Ber.*, 1931, **64**, 1981, footnote). The same criticism cannot be applied to the naming of the hexahydrophthalic acid series. Here the term *trans* is reasonable for the *DL*-acid as it denotes that the two functional groups are on opposite sides of the ring. It is true, however, that now that the ring is known to be multiplanar, these two " sides " no longer retain all their old precision.

Inversion of the 1 : 2-*Dimethylsuccinic Acids and their Derivatives.*—Key results are given in Table 2. Precise measurements of the various changes have not been made and it is not known whether the inversions are reversible. If so the equilibria must lie on the side indicated in the Table, which summarises broadly the direction of the changes. The corresponding data for the related cyclic acids, the hexahydrophthalic (see Ficken, France, and Linstead, following paper), have been added to Table 2 for comparison. Nitriles are omitted as no clear-cut inversion of them has been observed.

TABLE 2. *Inversion of dimethylsuccinic and hexahydrophthalic acids and their derivatives.*

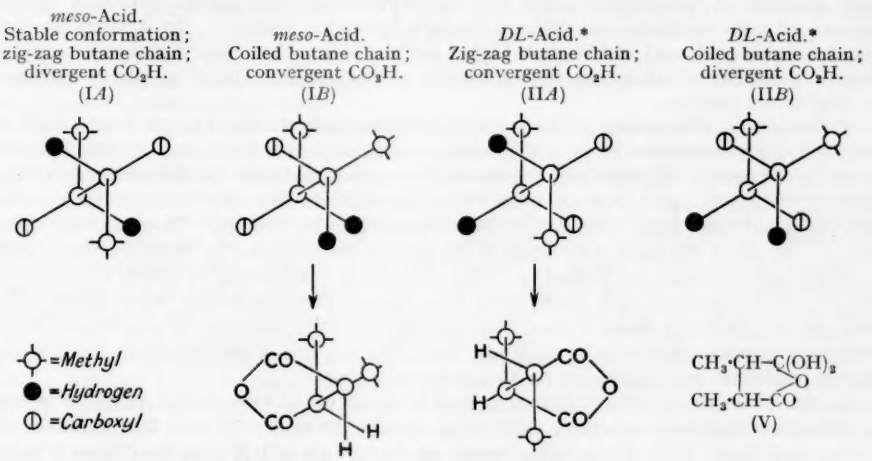
	αα'-Dimethylsuccinic	Hexahydrophthalic
Acid	*DL* → *meso*	*meso* → *DL* (*cis* → *trans*)
Diamide	*DL* → *meso*	*meso* → *DL*
Anhydride	*meso* → *DL*	*DL* → *meso* (*trans* → *cis*)
Imide	*meso* → *DL*	*DL* → *meso* [a]

[a] Attempts to make the *DL*-hexahydrophthalimide have so far only given the stable *meso*-isomeride (Ficken, France, and Linstead, *loc. cit.*).

Discussion.—A striking contrast between the aliphatic and the alicyclic compounds is at once apparent from Table 2. In the dimethylsuccinic series, the open-chain compounds are stable in the *meso*-form and their heterocyclic derivatives in the *DL*-forms, whereas in the hexahydrophthalic series the reverse is true. These facts can be accounted for as follows:

(1) The dimethylsuccinic acids would, in the absence of effects associated with the carboxyl groups, tend to take up a staggered conformation with a planar zig-zag arrangement of the butane chain. If a model of this is set up for the *meso*-acid, it will be seen (I*A*) that the carboxyl groups are at maximum divergence. If, on the other hand, the

carbon atoms of the *DL*-isomeride are arranged in a planar zig-zag conformation, the carboxyl groups come together (II*A*). Unless special factors operate, it is to be expected that the most favoured conformation will be that with the bulky groups as far apart as possible. The main special factors for the free acids might be attractive forces between the carboxyl groups. If these groups tend to come together by hydrogen bonding or, in the extreme case, by the formation of a dihydroxy-ring compound of the Anschütz type (V), then we could expect a departure from the requirements of the simple conformational argument. It is obvious, however, from empirical considerations that this is not true: if the favoured conformations of the acids were those with convergent carboxyl groups, the relative stabilities of the acids would be the same as those of their anhydrides. The reverse is true. It is concluded therefore that the acid which, *in its most favoured conformation*, can have a zig-zag butane chain and a divergent arrangement of carboxyls will be more stable than its isomeride. This is the *meso*-acid (I*A*) and in our view this is the explanation for its superior stability over the *DL*-isomeride, which must fluctuate between relatively unfavourable arrangements such as (II*A* and *B*). Conformation (I*A*)



* These diagrams correspond to only one enantiomorph, but this does not affect the argument.

represents, of course, only the most favoured, not the unique, arrangement for the *meso*-acid. The same basic arguments can be applied to the open-chain derivatives of the acids.

(2) The heterocyclic derivatives are different. In these the conformation of the acid with convergent carboxyl groups has in effect been stabilised (I*B* ⟶ III, II*A* ⟶ IV). When this is done in the *meso*-series, the methyl groups are brought into a coiled, *cis*-arrangement; whereas the anhydride of the *DL*-acid is formed with the methyl groups divergent and *trans* with respect to the hetero-ring. This explains the relative stability of the *DL*-anhydride and the imide.

(3) In the hexahydrophthalic series, these simple effects are complicated by the restraint placed upon the molecule by the substitution of the ring for the two methyl groups. Although some flexibility remains, the carbon substituents are no longer free to take up any position at will. The deciding factors are those which operate generally for 1 : 2-disubstituted derivatives of *cyclo*hexane. In the *DL*-series the two functional groups can both take up equatorial positions, but in the *meso*-series one is axial and the other equatorial. The former is accordingly the preferred arrangement.

(4) The data for the heterocyclic derivatives of the hexahydrophthalic acids are the least easy to interpret. The system is similar to that of the indan-1-ones in which the *cis*- is known to be more stable than the *trans*-form. Some factor is operating which makes the best arrangement for the *cis*-isomerides more stable than the best for the *trans*-isomerides. It is not known whether this favoured conformation contains a chair *cyclo*hexane ring fused to a somewhat puckered hetero-ring (perhaps with hydrogen bonding between carbonyl-oxygen and nuclear hydrogen atoms) or a boat *cyclo*hexane ring fused to a planar hetero-ring.

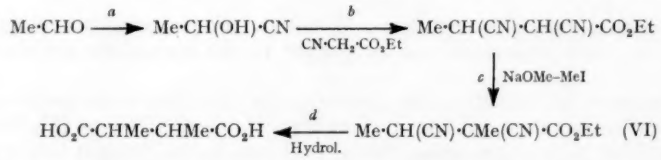
The treatment of the dimethylsuccinic acids given above (paras. 1 and 2) can clearly be applied to other aliphatic systems, although in many cases the results will be less clear-cut. Somewhat analogous arguments have been advanced to explain the effect of stereochemical factors on the ease of formation of cyclic acetals of polyhydric alcohols (Barker, Bourne, and Whiffen, *J.*, 1952, 3865).

On this basis both in the alicyclic and the dimethylsuccinic series the stable acids and amides have statistically the widest spread of the functional groups. The comparative steric freedom of the carboxyl and the carboxyamido-groups should permit a greater measure of intermolecular association through hydrogen bonding. In agreement with this, the stable acids and amides have higher melting points than their diastereoisomerides, whereas a similar effect is not shown by the corresponding nitriles in which hydrogen bonding is not possible.

A Note on the Preparative Methods for Dimethylsuccinic Acids.—On pp. 3722—3733 we described the preparation of pure diastereoisomeric materials from the mixture of acids normally obtained. We now add a note on the various methods for the synthesis of this mixture. Three broad routes are open: (1) The condensation of α-bromopropionic ester with ethyl sodiomalonate, followed by methylation and hydrolysis. There are numerous variants, of which the most interesting is the process investigated by Zelinsky (*Ber.*, 1888, **21**, 3160) and by Bone and Perkin (*J.*, 1896, **69**, 63 etc.), according to which the action of cyanide on α-bromopropionic ester gives some dimethylcyanosuccinic ester direct. Our work on the Zelinsky–Bone–Perkin process and on other variants of the bromo-ester–sodio-ester reaction leads us to conclude that they are less attractive than the Higson–Thorpe procedure (see below) for routine preparative work.

As the molecule of dimethylsuccinic acid is made up of two similar parts, it is easy to formulate synthetic schemes, depending on the twinning of two free radicals (cf. Fichter and Heer, *Helv. Chim. Acta*, 1936, **19**, 149): $2Me{\cdot}\dot{C}HX \longrightarrow Me{\cdot}CHX{\cdot}CHX{\cdot}Me$. Exploratory investigation of a number of such processes has yielded nothing of preparative value.

Our preferred process is as illustrated. Acetaldehyde cyanohydrin was prepared in excellent and reproducible yield by the use of piperidine as catalyst. Stages (*b*) and (*c*),



which could be carried out in one series of operations, followed Higson andThorpe (*loc. cit.*). The overall yield of αβ-dicyano-α-methylbutyric ester (VI) was 75%. Complete hydrolysis then gave a mixture of the stereoisomeric αα′-dimethylsuccinic acids in nearly theoretical yield and approximately equal proportions.

In view of our requirement for dimethylsuccinonitrile, the partial hydrolysis of the dicyano-ester (VI) was also examined. Treatment of this material with cold methanolic potassium hydroxide deposited some insoluble potassium salt but the bulk of the product remained in solution. After removal of the insoluble salt, attempts were made to isolate the dicyanomethylbutyric acid corresponding to (VI), but these failed owing to the onset of decarboxylation. This was accordingly completed by vacuum-distillation. The viscous

distillate deposited some solid *DL*-αα′-dimethylsuccinonitrile, identified by hydrolysis to the *DL*-acid and by comparison with that already described. The uncrystallisable residue from the solid dinitrile was a mixture of *meso*- and *DL*-isomers. If the potassium salt was not removed before this process was carried out, the dinitrile obtained was contaminated with *DL*-imide and some αα′-dimethylsuccinamic acid (mainly *meso*). The potassium salt on acidification yielded αβ-dicyano-α-methylbutyric acid hydrate, the acid corresponding to the ester (VI). The acid, on hydrolysis, gave a mixture of dimethylsuccinic acids, mainly *meso*. Decarboxylation by heat afforded a mixture of αα′-dimethylsuccinonitriles, the *meso*-form again predominating. The sythesis thus provides both αα′-dimethylsuccinonitriles, although only the *DL*-form was obtained pure, but is far inferior to that involving dehydration of the diamides by carbonyl chloride.

Experimental

Acetaldehyde Cyanohydrin.—Acetaldehyde (50 g.) was added dropwise to liquid hydrogen cyanide (49 c.c.) and piperidine (2·5 c.c.). The mixture was left at about 10° overnight. Concentrated sulphuric acid (2·5 c.c.) was then added and the mixture distilled, giving acetaldehyde cyanohydrin (68 g., 85%), b. p. 102°/30 mm. We are indebted to Imperial Chemical Industries Limited, Dyestuffs Division, for communication of this considerable improvement on literature methods.

Partial Hydrolysis of Ethyl αβ-Dicyano-α-methylbutyrate (VI).—(a) *αα′-Dimethylsuccinonitrile.* The ester (40 g.), prepared from acetaldehyde cyanohydrin and ethyl cyanoacetate, followed by methylation (Higson and Thorpe, *loc. cit.*), was added to potassium hydroxide (14 g.) in methanol (40 c.c.), and the solution left at room temperature for 48 hr. The crystalline solid A was separated. Most of the methanol was evaporated under reduced pressure, the residue dissolved in water (40 c.c.), and the solution extracted with ether overnight. Hydrolysis, with concentrated hydrochloric acid, of the oil extracted by the ether gave *meso*-αα′-dimethylsuccinic acid (1·5 g.), m. p. 195—197°. The aqueous layer was acidified with concentrated hydrochloric acid and extracted with ether overnight. The viscous oil obtained after concentration of the ether extract was distilled (b. p. 95—110°/1 mm.), decarboxylation occurring. The distillate (5·1 g.) was dissolved in light petroleum (b. p. 60—80°) and ethanol, and the solution frozen in liquid nitrogen. As the mixture warmed, the solid was filtered off, the process being repeated until no more solid, m. p. 41—43°, was obtained. The solid was recrystallised from light petroleum–ethanol or from water, giving colourless prisms of *DL*-αα′-*dimethylsuccinonitrile* (1·4 g., 6%), m. p. 56—58° (Found: C, 66·8; H, 6·9; N, 25·7. $C_6H_8N_2$ requires C, 66·6; H, 7·5; N, 25·9%). *DL*-Dimethylsuccinonitrile (102 mg.) was refluxed for 2 hr. with concentrated hydrochloric acid (3 c.c.). *DL*-αα′-Dimethylsuccinic acid (98 mg., 71%), m. p. 125—127°, separated.

The uncrystallisable residue contained *meso*-material, and hydrolysis of 1 g. with concentrated hydrochloric acid gave 520 mg. of *meso*-αα′-dimethylsuccinic acid and 340 mg. of the *DL*-acid.

(b) αβ-*Dicyano-α-methylbutyric acid.* The yield of the potassium salt A was greater in small-scale experiments, less heat being generated to cause decarboxylation. Ethyl αβ-dicyano-α-methylbutyrate (136·5 g.) was divided into 14 batches, each of which was treated with potassium hydroxide (3·5 g.) in methanol (35 c.c.). After 3 hr. at room temperature the solutions were cooled in ice for 30 min. and the precipitates collected. The dried potassium salt was dissolved in the minimum amount of water, and the solution filtered through kieselguhr and acidified with hydrochloric acid. The solid was collected, dried (18·2 g., 14%), and crystallised from ethanol–ether, giving αβ-*dicyano-α-methylbutyric acid monohydrate*, m. p. 175—177° (with evolution of carbon dioxide) (Found: C, 49·2; H, 6·1; N, 16·4. $C_7H_{10}O_3N_2$ requires C, 49·4; H, 5·9; N, 16·5%). The acid (500 mg.) was hydrolysed with concentrated hydrochloric acid (5 c.c.), giving *meso*- (380 mg.; m. p. 193°) and *DL*-dimethylsuccinic acid (130 mg.; m. p. 104—109°) (see below).

(c) *Decarboxylation of αβ-dicyano-α-methylbutyric acid.* The acid (1·0 g.) was heated at 170° under reduced pressure for 20 min. Vigorous evolution of carbon dioxide occurred and a colourless substance sublimed (m. p. 40—42°; 231 mg., 36%). The substance was resublimed at atmospheric pressure and twice crystallised from water, giving a mixture of *meso*- and *DL*-αα′-dimethylsuccinonitrile, m. p. 41—43° (Found: C, 66·5; H, 7·6; N, 25·5. Calc. for

$C_6H_8N_2$: C, 66·6; H, 7·5; N, 25·9%). Hydrolysis of the nitrile (100 mg.) with concentrated hydrochloric acid (2 c.c.) gave *meso*-αα′-dimethylsuccinic acid (82 mg., 61%), m. p. 189—193°.

(d) *αα′-Dimethylsuccinamic acids.* If the potassium salt A was not removed from the reaction mixture before acidification of the hydrolysate, the *DL*-αα′-dimethylsuccinonitrile was contaminated with *DL*-αα′-dimethylsuccinimide, m. p. 104—106°, and with αα′-dimethylsuccinamic acids; the acids were separated from the imide by means of sodium carbonate solution, reprecipitated with hydrochloric acid, and crystallised from ethanol; they had m. p. 153—158° (Found: C, 49·3; H, 7·6; N, 10·4. Calc. for $C_6H_{11}O_3N$: C, 49·6; H, 7·6; N, 9·7%). Hückel and Müller (*Ber.*, 1931, **64**, 1989) give m. p. 165—167° for *meso*-αα′-dimethylsuccinamic acid, and m. p. 148—149° for the *DL*-acid. αα′-Dimethylsuccinamic acid (170 mg.) on hydrolysis with concentrated hydrochloric acid (3 c.c.) gave *meso*-αα′-dimethylsuccinic acid (80 mg., 47%).

αα′-Dimethylsuccinamic acid (107 mg.) was warmed on the steam-bath with acetyl chloride (8 drops) for 4 hr. A little water was added and the solution extracted with ether. The oily residue, after evaporation of the ether, was sublimed, giving *DL*-αα′-dimethylsuccinimide, m. p. and mixed m. p. 103—105°.

Complete Hydrolysis of Ethyl αβ-Dicyano-α-methylbutyrate.—The ester (50 g.) was refluxed with concentrated hydrochloric acid (300 c.c.) for 24 hr. On cooling, *meso*-αα′-dimethylsuccinic acid (15 g., 38%), m. p. 198—202°, crystallised. Recrystallisation several times from water and from concentrated hydrochloric acid gave pure *meso*-acid, m. p. 209°. Continuous ether-extraction of the filtrate overnight gave the remainder of the αα′-dimethylsuccinic acid (*DL* and some *meso*) (19·5 g., 48%).

Separation of meso- *and* DL-αα′-*Dimethylsuccinic Acids.*—Mixed αα′-dimethylsuccinonitriles (1·0 g.) and concentrated hydrochloric acid (5 c.c.) were refluxed for 2 hr., then cooled; *meso*-αα′-dimethylsuccinic acid (520 mg.), m. p. 193—195°, separated. The filtrate was extracted with ether overnight and the ether removed. The residue was cooled in ice and treated with 2—3 drops of cold water, and the remaining solid (47 mg.), m. p. 130—135° (a mixture of *meso* and *DL*), was filtered off. The water was removed from the filtrate in a vacuum-desiccator, and the gummy residue recrystallised from concentrated hydrochloric acid, giving *DL*-αα′-dimethylsuccinic acid (340 mg.), m. p. 123—127°.

Isomerisation of DL-αα′-*Dimethylsuccinic Acid.*—*DL*-αα′-Dimethylsuccinic acid (100 mg.) was refluxed with concentrated hydrochloric acid for 40 hr. The hydrochloric acid was removed and the residue crystallised from water, to give *meso*-αα′-dimethylsuccinic acid (5 mg.; 5% conversion), m. p. 191—193°.

DL-αα′-*Dimethylsuccinimide.*—Mixed *meso*- and *DL*-αα′-dimethylsuccinic acids (30 g.) were dissolved in aqueous ammonia (*d* 0·880; 45 c.c.), and the mixture distilled. The fraction of b. p. <110° was rejected, most of the imide distilling at 240—260°. The oily distillate was crystallised twice from water, giving colourless prisms of *DL*-αα′-dimethylsuccinimide (17·5 g., 71%), m. p. 107—109° (Found: N, 10·8. Calc. for $C_6H_9O_2N$: N, 11·0%). The imide (50 mg.) was refluxed with concentrated hydrochloric acid (2 c.c.) for 2 hr., *DL*-αα′-dimethylsuccinic acid (45 mg., 78%), m. p. 125—127°, separating on cooling.

DL-αα′-*Dimethylsuccinamide.*—(*a*) *DL*-αα′-Dimethylsuccinimide (2·0 g.) was dissolved in aqueous ammonia (*d* 0·880; 8 c.c.), and the solution kept at room temperature for 48 hr. *DL*-αα′-Dimethylsuccinamide was filtered off and washed well with cold water and with methanol to remove traces of unchanged imide. The yield of amide was 1·44 g. (64%) and the m. p. 221—223° (Found: C, 50·0; H, 8·5; N, 20·0. Calc. for $C_6H_{12}O_2N_2$: C, 50·0; H, 8·4; N, 19·4%) (Morrell, *J.*, 1914, **105**, 2698, gives m. p. 238°). Attempts to recrystallise the diamide from water, glacial acetic acid, or dilute acetic acid invariably led to partial isomerisation to the *meso*-amide.

(*b*) *DL*-αα′-Dimethylsuccinimide (1·0 g.) was heated with methanolic ammonia (5 c.c.) (prepared from 5 c.c. of methanol and 5 c.c. of liquid ammonia) in a sealed tube at 90° for 8 hr. After evaporation of the ammonia, *DL*-αα′-dimethylsuccinamide (0·81 g., 72%), m. p. 221—223°, was collected.

DL-αα′-Dimethylsuccinamide (198 mg.) was refluxed with concentrated hydrochloric acid (4 c.c.) for 2 hr. *DL*-αα′-Dimethylsuccinic acid (120 mg., 60%), m. p. 125—127°, separated on cooling. The *DL*-amide (112 mg.) was heated at 220° until evolution of ammonia ceased. The residue was sublimed under reduced pressure, yielding *DL*-αα′-dimethylsuccinimide (69 mg., 70%), m. p. 104—106°.

DL-αα′-*Dimethylsuccinonitrile.*—*DL*-Dimethylsuccinamide (50·5 g.) was suspended in dry pyridine (610 c.c.), and carbonyl chloride (about 87 g.; dried by passage through concentrated

sulphuric acid) was bubbled into the rapidly stirred solution. The temperature was kept at 60—70° by control of the rate of gas-flow. The solution was allowed to cool for 3 hr., poured on ice, and made acid to Congo-red with concentrated hydrochloric acid. The dark red solution was continuously extracted with ether for several days, and the ether extracts were evaporated. *DL*-αα′-Dimethylsuccinonitrile (28·1 g., 75%), m. p. 48—51°, was obtained by crystallisation of the residue from water (charcoal). Further crystallisation from ethanol–light petroleum (b. p. 60—80°) raised the m. p. to 57—59°. The mixed m. p. with *DL*-αα′-dimethylsuccinonitrile, obtained by hydrolysis of ethyl αβ-dicyano-α-methylbutyrate, was undepressed (Found : C, 66·3; H, 7·6. Calc. for $C_6H_8N_2$: C, 66·6; H, 7·5%).

A small amount of uncrystallisable oil (2·1 g.) gave *meso*-αα′-dimethylsuccinic acid (0·6 g.), m. p. 191—195°, on hydrolysis with concentrated hydrochloric acid.

DL-αα′-Dimethylsuccinonitrile (110 mg.; prepared from diamide) on hydrolysis with concentrated hydrochloric acid (1·5 c.c.) gave *DL*-αα′-dimethylsuccinic acid (103 mg., 70%), m. p. 126—127°. The *DL*-nitrile was not isomerised when refluxed with phosphorus oxychloride in pyridine.

Dimethyl meso-αα′-*Dimethylsuccinate.*—*meso*-αα′-Dimethylsuccinic acid (13 g.), m. p. 193—196°, methanol (25 c.c.), benzene (50 c.c.), and concentrated sulphuric acid (5 c.c.) were refluxed for 7 hr. and then cooled. The benzene layer was shaken with sodium carbonate solution and water, and dried (Na_2SO_4). Evaporation of the benzene and distillation of the residue gave dimethyl *meso*-αα′-dimethylsuccinate (12 g., 80%), b. p. 110—112°/35 mm. Hydrolysis of the *meso*-ester (1·2 g.) with concentrated hydrochloric acid gave *meso*-acid (0·8 g., 80%), m. p. 204—206°.

meso-αα′-*Dimethylsuccinamide.*—Methanol was added to a mixture of dimethyl *meso*-αα′-dimethylsuccinate (31·5 g.) and aqueous ammonia (*d* 0·880; 90 c.c.) until the mixture became homogeneous. The solution was heated at 165° for 5 days. After evaporation of some of the ammonia and methanol, a solid, m. p. 290—293°, separated. Recrystallisation from glacial acetic acid gave colourless prisms of *meso*-αα′-dimethylsuccinamide (5·4 g., 21%), m. p. 300—302° (Found : C, 49·7; H, 8·4; N, 19·0. Calc. for $C_6H_{12}O_2N_2$: C, 50·0; H, 8·4; N, 19·4%) (Morrell, *loc. cit.*, gives m. p. 244°).

meso-αα′-Dimethylsuccinamide (104 mg.) was hydrolysed with concentrated hydrochloric acid (2 c.c.), giving *meso*-αα′-dimethylsuccinic acid, m. p. 201—204°.

meso-αα′-*Dimethylsuccinonitrile.*—*meso*-αα′-Dimethylsuccinamide (5·4 g.) was suspended in pyridine and treated with carbonyl chloride (about 9 g.) as for the *DL*-amide. Continuous ether-extraction of the resulting solution for 48 hr. gave a viscous oil which partly crystallised during 3 weeks. The solid was separated from the oil and crystallised twice (charcoal) from water, to give colourless needles of meso-αα′-*dimethylsuccinonitrile* (0·51 g., 13%), m. p. 45—46°, and mixed m. p. 43—44° with *DL*-αα′-dimethylsuccinonitrile (m. p. 57—59°) (Found : C, 66·4; H, 7·4; N, 26·1. $C_6H_8N_2$ requires C, 66·6; H, 7·5; N, 25·9%).

meso-αα′-Dimethylsuccinonitrile (50 mg.) gave on hydrolysis with concentrated hydrochloric acid (2 c.c.), *meso*-αα′-dimethylsuccinic acid (52 mg., 77%), m. p. 201—204°.

meso-αα′-*Dimethylsuccinic Anhydride* (with P. Walker).—Sodium *meso*-αα′-dimethylsuccinate (2·7 g.) was suspended in dry ether (40 c.c.), and thionyl chloride (1·5 c.c.) added dropwise with shaking. The mixture was kept overnight in a desiccator, and the sodium chloride removed by centrifugation. The resulting solution gave *meso*-αα′-dimethylsuccinic anhydride (1·35 g., 74%), m. p. 39—40°, on evaporation. Attempted recrystallisation of the anhydride from benzene gave anhydride containing *meso*-acid. An ethereal solution of anhydride slowly deposited *meso*-acid.

meso-αα′-Dimethylsuccinic anhydride (0·1 g.) was hydrolysed with concentrated hydrochloric acid (0·2 c.c.), giving *meso*-αα′-dimethylsuccinic acid, m. p. 198—199°.

meso-αα′-*Dimethylsuccinimide.*—Dimethylmaleinimide (459 mg.) in ethanol (10 c.c.) was shaken under hydrogen with Adams platinum oxide catalyst (23 mg.) for 30 min. during which 1 mol. of hydrogen was taken up. The catalyst was removed and the filtrate evaporated to dryness at room temperature. The remaining oil slowly crystallised, giving *meso*-αα′-dimethylsuccinimide (426 mg., 92%), m. p. 45—47° (Found : C, 56·5; H, 7·2; N, 11·6. Calc. for $C_6H_9O_2N$: C, 56·7; H, 7·1; N, 11·0%).

Hydrolysis of the *meso*-imide (117 mg.) with concentrated hydrochloric acid (1 c.c.) gave *meso*-αα′-dimethylsuccinic acid (98 mg., 75%), m. p. 202—205°.

Mixtures of the two dimethylsuccinimides melted at the following temperatures :

meso (%)	0	10	20	30	40	50	60	70	80	90	100
M. p.	107°	84°	79°	60°	52°	45°	39°	34°	32°	37°	45°

Sublimation of the *meso*-imide gave a mixture, m. p. 78—84°, which was hydrolysed to a mixture of αα′-dimethylsuccinic acids (mainly *DL*), m. p. 107—121°. The sublimed imide was estimated from the mixed m. p. curve to contain 87% of the *DL*-isomer.

Analyses in this and the following paper were carried out in the Microanalytical Laboratory (Mr. F. H. Oliver) of this Department.

Department of Organic Chemistry, Imperial College of Science and Technology, South Kensington, London, S.W.7. [*Received, June 2nd,* 1954.]

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1 : 2-*Dicarboxylic Acids. Part III.* Nitrogenous Derivatives of the Isomeric Hexahydrophthalic Acids and of* 3 : 4 : 5 : 6-*Tetrahydrophthalic Acid.*

By G. E. Ficken, H. France, and R. P. Linstead.

[Reprint Order No. 5434.]

Imides, diamides, and dinitriles of these acids are described, together with certain other derivatives. It is shown that among derivatives of the geometrically isomeric saturated acids, the expected stereochemical relations hold and that the *trans*-forms of simple derivatives are more stable; whereas when an *ortho*-heterocyclic ring is present the *cis*-isomeride is the more stable.

The discovery of the imidines (see, for example, Elvidge and Linstead, *J.*, 1952, 5000; 1954, 442) and the opening of a new route to azaporphins has prompted an investigation into the imidines derived from hexahydro- and 3 : 4 : 5 : 6-tetrahydro-phthalic acid. This has involved a preliminary study of the nitrogenous derivatives of these acids, which is described in the present paper.

Hexahydrophthalic Series.—The relative stabilities of the *cis*- and the *trans*-forms of cyclic and acyclic derivatives of the hexahydrophthalic acids have been of interest for over 60 years. It is well known from the work of von Baeyer and of Hückel that the acids, esters, and anhydrides can be obtained in two forms; that in the acids and esters the *trans*-form is the more stable, but that of the two anhydrides the *cis* is the more stable. Hückel and Müller (*Ber.*, 1931, **64**, 1981) found that the imide system behaved like the anhydride. Our work supports this and shows that, in general, the nitrogenous derivatives behave like their oxygen counterparts. Where there is no *ortho*-ring the *cis*-form is either the only isomer which can be isolated or the more stable of the pair.

cis-Hexahydrophthalimide (I) is most easily prepared by fusion of the corresponding anhydride with urea. The product, m. p. 137°, is identical with material prepared by catalytic hydrogenation of phthalimide (Willstätter and Jacquet, *Ber.*, 1918, **51**, 767; Vavon and Peignier, *Bull. Soc. chim.*, 1929, **45**, 296; Hückel and Müller, *Ber., loc. cit.*). The *cis*-configuration was postulated by Willstätter and proved by Hückel. Sircar (*J.*, 1927, 1252) reported that distillation of the ammonium salt of *cis*- or *trans*-hexahydrophthalic acid gave a *trans*-imide of m. p. 164°. Hückel and Müller pointed out the improbability of this observation and were unable to repeat it, their product being the *cis*-imide contaminated with a product of m. p. 167°. The constitution of the latter was not fully established but it was not a hexahydrophthalimide.

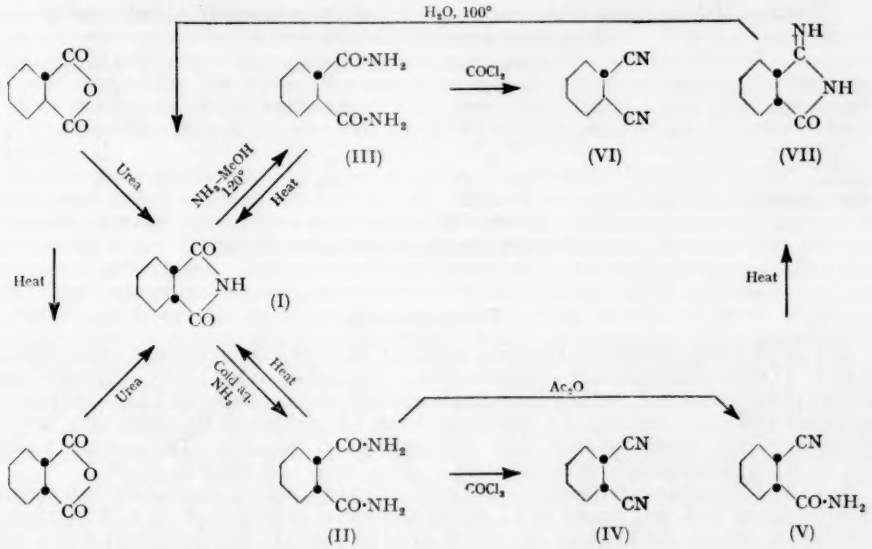
We find that the *cis*-imide is obtained alike by distillation of ammonium *trans*-hexahydrophthalate, the fusion of *trans*-hexahydrophthalic anhydride with urea, or by the action of heat on the diamide of either the *cis*- or the *trans*-acid. It is clear therefore that the *cis* is the thermally stable imide and that Sircar's observation is erroneous.

The *cis*-imide reacted slowly at room temperature with aqueous ammonia to give the *cis*-amide (II), m. p. 190—191°. At 120° with methanolic ammonia, however, an inversion

* Part II, preceding paper.

of configuration occurred, the *cis*-imide giving the *trans*-amide (III), m. p. 281—282°. Price and Schwarcz (*J. Amer. Chem. Soc.*, 1940, **62**, 2891) were unable to prepare these diamides from the corresponding diesters by the action of ethanolic ammonia at room temperature. We find, however, that dimethyl *trans*-hexahydrophthalate slowly reacts with aqueous ammonia at room temperature or with methanolic ammonia at 100°, to give the *trans*-diamide.

Dehydration of the *cis*-amide with acetic anhydride gave either *cis*-hexahydrophthalonitrile (IV) or the corresponding *cis*-cyano-amide (V) according to the length of treatment. The *cis*-dinitrile was better prepared, in almost quantitative yield, by dehydration of the *cis*-amide with carbonyl chloride. The same reagent dehydrated the *trans*-amide to the



trans-dinitrile (VI). The configurations and homogeneity of all these compounds were established by hydrolysis to the parent acids under non-inverting conditions. We have been unable to effect interconversion of the two dinitriles. Both dinitriles are crystalline and it is of interest that the usual relations between the melting points (*trans*>*cis*) which holds for example for the acids, amides, and anilides is reversed for the dinitriles, the *cis*-form of which melts at 64°, 12° above the *trans*. The same feature has been encountered among the derivatives of the $\alpha\alpha'$-dimethylsuccinic acids (Linstead and Whalley, preceding paper).

Many years ago, hexahydrophthalonitrile had been prepared in these laboratories by Dr. K. Sams (Thesis, London, 1934) by another route : *cyclo*hexanone cyanohydrin was dehydrated to 3 : 4 : 5 : 6-tetrahydrobenzonitrile which by the action of hydrogen cyanide yielded hexahydrophthalonitrile as a non-crystalline mass of m. p. about 42—46°. This material has been re-examined and is found to be a mixture of the two geometrical isomerides (IV and VI).

When *cis*-2-cyanohexahydrobenzamide was fused it changed into the isomeric octahydro-1-imino-3-oxo*iso*indole (VII), the reaction being analogous to the thermal isomerisation of *o*-cyanobenzamide (Braun and Tcherniac, *Ber.*, 1907, **40**, 2709). The cyclic imino-imide (which forms a picrate and a monohydrochloride) has the *cis*-configuration and readily gives *cis*-hexahydrophthalimide on hydrolysis with boiling water. The corresponding di-imine (hexahydrophthalimidine) is also stable in the *cis*-configuration.

Four examples are thus known (anhydride, imide, imino-imide, and imidine) of cyclic

derivatives of hexahydrophthalic acid stable in the *cis*-form.* These results are discussed in the preceding paper.

3 : 4 : 5 : 6-*Tetrahydrophthalic Series.*—Most of the essential nitrogenous intermediates have already been described (Ficken and Linstead, *J.*, 1952, 4846). Their preparation has been improved in two respects. First, 3 : 4 : 5 : 6-tetrahydrophthalic anhydride can be readily obtained by the catalytic isomerisation of its 1 : 2 : 3 : 6-isomeride over palladium.† Secondly, for the dehydration of Δ^1-diamide to Δ^1-dinitrile, carbonyl chloride is to be preferred to the phosphoric oxide–triethylamine reagent used in our previous work.

The properties of the various derivatives of the three series are summarised in the Table, and the main reactions in the Chart.

TABLE. *Melting points of derivatives of* cis- *and* trans-*hexahydrophthalic and of* 3 : 4 : 5 : 6-*tetrahydrophthalic acid.*

	cis-Hexahydro	*trans*-Hexahydro	3 : 4 : 5 : 6-Tetrahydro
Diacids	192°	227—229°	120°
Diamides	190—191	281—282	220 *
Cyanoamides	143—145	—	169—170
Dinitriles	63—65	51—53	97
Anhydrides	32	144—145	72
Imides	136—137	Labile	172
Imino-imides	227—229 (picrate, 205)	—	200—202 (picrate, 190)

* Rapid heating in sealed tube.

EXPERIMENTAL

3 : 4 : 5 : 6-*Tetrahydrophthalic Anhydride from* cis-1 : 2 : 3 : 6-*Tetrahydrophthalic Anhydride.*—*cis*-1 : 2 : 3 : 6-Tetrahydrophthalic anhydride (200 g.) was heated to 200—210°, 20% palladium–charcoal (1·8 g.) was added, and heating at this temperature was continued for 3 hr. The product was boiled with water (500 ml.), the solution evaporated to dryness on the steam-bath, and the residue extracted repeatedly with light petroleum (b. p. 60—80°). The extracts yielded 3 : 4 : 5 : 6-tetrahydrophthalic anhydride (151 g., 76%), m. p. and mixed m. p. 70°.

3 : 4 : 5 : 6-*Tetrahydrophthalonitrile.*—Carbonyl chloride, dried by passage through concentrated sulphuric acid, was passed into a stirred suspension of 60 g. of 3 : 4 : 5 : 6-tetrahydrophthalamide (Ficken and Linstead, *loc. cit.*) in pyridine (500 ml.) in a flask fitted with a wide air-condenser and a thermometer dipping into the liquid. The flask was heated in a water-bath, which was removed as soon as the internal temperature reached 60°. A strongly exothermic reaction occurred; the temperature rose rapidly to 75—80° and was maintained in this range by adjusting the rate of flow of carbonyl chloride. Passage of gas was continued until the temperature began to fall, by which time an increase in weight of about 100 g. had occurred. The mixture was allowed to cool to room temperature, and the dark brown, viscous product was added cautiously to crushed ice (1 kg.), and the solution was neutralised (Congo-red) with hydrochloric acid and continuously extracted with ether for several days. The extract was washed with a little saturated salt solution, and dried (Na_2SO_4); the ether was removed, and the residue distilled at 204°/50 mm. The yield of tetrahydrophthalonitrile was 30 g. (64%) and after crystallisation from aqueous ethanol the m. p. and mixed m. p. were 97°.

cis-*Hexahydrophthalimide* (I).—*cis*-Hexahydrophthalic anhydride, prepared in 94% yield by hydrogenation of *cis*-1 : 2 : 3 : 6-tetrahydrophthalic anhydride in the presence of a platinum catalyst (Jenkins and Costello, *J. Amer. Chem. Soc.*, 1946, **68**, 2733), had m. p. 30°, and on hydrolysis yielded *cis*-hexahydrophthalic acid, m. p. 190—192° (decomp.).

The *cis*-anhydride (277 g.) and urea (60 g.) were heated together at 160° until a vigorous reaction occurred; then the heating-bath was removed. When the reaction slackened the mixture was reheated for a further 30 min., and poured with vigorous stirring into ice and water (1 kg.). The white *cis*-hexahydrophthalimide was filtered off and washed with water. The yield was 217 g. (78%) and the m. p. of the crude product was 134—136°, raised by crystallisation

* Since this was written, a further example—that of *cis*-hexahydro-*N*-methylphthalimide—has been reported (Bailey, Haworth, and McKenna, *J.*, 1954, 969). Compare also the *N*-phenylimides prepared by Stoermer and Steinbeck (*Ber.*, 1932, **65**, 413).

† This unusual rearrangement is being further investigated by Mr. K. D. Whiting in this Department.

from water to 136—137° (Hückel and Müller, *loc. cit.*, give m. p. 137°) (Found : N, 9·2. Calc. for $C_8H_{11}O_2N$: N, 9·1%).

cis-*Hexahydrophthalamide* (II).—Finely powdered *cis*-hexahydrophthalimide (146 g.) was added to aqueous ammonia (450 ml.) saturated at 0°, and the mixture left at this temperature for 7 days. The white crystalline precipitate of cis-*hexahydrophthalamide* (125 g.) was filtered off; the m. p. was 190—191° (decomp.), unchanged by crystallisation from dilute aqueous ammonia (Found : C, 56·3; H, 8·4; N, 16·2. $C_8H_{14}O_2N_2$ requires C, 56·45; H, 8·3; N, 16·5%). The filtrate from the above preparation was evaporated to dryness and the residue was heated at 170° for 1 hr., to give *cis*-hexahydrophthalimide (24 g.). With allowance for this recovered imide, the yield of diamide was 92%. When the diamide was heated just above its m. p., ammonia was evolved; the product on crystallisation from acetone gave *cis*-hexahydrophthalimide, m. p. and mixed m. p. 135—136°. On hydrolysis with 2N-nitric acid for 15 hr. the diamide yielded almost pure *cis*-hexahydrophthalic acid, m. p. 184—187°, mixed m. p. 185—188°.

cis-2-*Cyanohexahydrobenzamide* (V).—*cis*-Hexahydrophthalamide (30·0 g.) and acetic anhydride (60 ml.) were refluxed together vigorously for 10 min., and the solution was cooled and poured into ether (500 ml.). The white precipitate of cis-2-*cyanohexahydrobenzamide* (9·7 g., 36%) was filtered off and washed with ether; after crystallisation from ethyl acetate the m. p. was 143—145° (Found : C, 63·1; H, 7·9; N, 18·3. $C_8H_{12}ON_2$ requires C, 63·1; H, 7·95; N, 18·4%).

cis-*Hexahydrophthalonitrile.*—(a) *Acetic anhydride. cis*-Hexahydrophthalamide (5·3 g.) and acetic anhydride (25 ml.) were refluxed for 4 hr. Most of the acetic acid and anhydride were distilled out and the residue was boiled with water (100 ml.) containing sufficient ammonia to neutralise the acid. The aqueous solution was decanted from a small amount of dark, viscous material and cooled in ice. The white solid was filtered off, washed with a little cold water, and dried. The yield of cis-*hexahydrophthalonitrile* (IV) was 970 mg. (21%) and the m. p. was 52—53°, raised to 63—65° by sublimation (Found : C, 71·8; H, 7·6; N, 20·65. $C_8H_{10}N_2$ requires C, 71·6; H, 7·5; N, 20·9%). The nitrile (440 mg.) on hydrolysis with boiling 2N-nitric acid yielded an acid (410 mg.), m. p. and mixed m. p. with *cis*-hexahydrophthalic acid, 186—189°. The dianilide (prepared according to Linstead, Davis, and Whetstone, *J. Amer. Chem. Soc.*, 1942, **64**, 2013) had m. p. and mixed m. p. with *cis*-hexahydrophthalanilide, 237—238°.

(b) *Carbonyl chloride. cis*-Hexahydrophthalamide (81 g.) was dehydrated with carbonyl chloride, as described for the tetrahydrophthalamide, except that the temperature was kept at 60—65°. The product from the ether-extraction distilled at 130—131·5°/0·7 mm. The distillate had m. p. 63—65°, undepressed by admixture with the product obtained by acetic anhydride dehydration. The yield of *cis*-hexahydrophthalonitrile was 61 g. (95%). In another experiment, where the temperature was allowed to rise to 90°, the product did not solidify completely after distillation, indicating the presence of a certain amount of *trans*-dinitrile; hydrolysis yielded an acid, m. p. 171—184°.

trans-*Hexahydrophthalamide.*—(*a*) Dimethyl *trans*-hexahydrophthalate, prepared by isomerisation of the mixture of isomerides obtained by catalytic hydrogenation of dimethyl phthalate (Price and Schwarcz, *loc. cit.*; cf. Haggis and Owen, *J.*, 1953, 389), had b. p. 143°/28 mm., m. p. 28°; on hydrolysis with ethanolic potassium hydroxide it yielded *trans*-hexahydrophthalic acid, m. p. 225—227°. The *trans*-ester (9·8 g.) was mixed with aqueous ammonia (*d*, 0·880; 30 ml.) and sufficient methanol to form a homogeneous solution. This was left for 5 days at room temperature, then the precipitated solid was filtered off (690 mg.). trans-*Hexahydrophthalamide* (III) formed colourless needles from aqueous ethanol, m. p. 281—282° (decomp.) (Found : C, 56·3; H, 8·3; N, 16·7. $C_8H_{14}O_2N_2$ requires C, 56·45; H, 8·3; N, 16·5%). The filtrate from the above preparation slowly deposited further amounts of the diamide, and after 35 weeks a total of 4·0 g. (37%) had been obtained. On hydrolysis with 2N-nitric acid it yielded an acid, m. p. 221—225°, mixed m. p. 223—226° with *trans*-hexahydrophthalic acid. When heated above its m. p., the *trans*-diamide evolved ammonia, the product being the *cis*-imide, m. p. and mixed m. p. 133—136°. When the *trans*-ester was heated with methanolic ammonia at 120° for 18 hr., only 3% of the diamide and much unchanged ester were obtained.

(*b*) *cis*-Hexahydrophthalimide (16·6 g.) was heated for 24 hr. in an autoclave at 120° with methanol (100 ml.) containing ammonia (50 ml. of liquid). The solid was filtered off and washed with methanol, to yield *trans*-hexahydrophthalamide (16·3 g., 89%), m. p. and mixed m. p. 281—282° (decomp.).

trans-*Hexahydrophthalonitrile.*—*trans*-Hexahydrophthalamide (11·8 g.) was dehydrated with carbonyl chloride as for the *cis*-diamide. The product obtained by ether-extraction crystallised from light petroleum (b. p. 40—60°), to yield trans-*hexahydrophthalonitrile* (VI)

(8·4 g., 90%), m. p. 51—53° unchanged after sublimation (Found : C, 71·6; H, 7·5; N, 21·4. $C_8H_{10}N_2$ requires C, 71·6; H, 7·5; N, 20·9%). The mixed m. p. with the *cis*-dinitrile was 40—47°. The nitrile (540 mg.) on hydrolysis with 2N-nitric acid yielded an acid (660 mg.), m. p. 222—225°, mixed m. p. 224—227° with *trans*-hexahydrophthalic acid. The dianilide had m. p. and mixed m. p. with *trans*-hexahydrophthalanilide (Linstead, Davis, and Whetstone, *loc. cit.*), 314—315°.

Attempted Interconversion of the Dinitriles.—No isomerisation occurred when either *cis*- or *trans*-hexahydrophthalonitrile was subjected to the following conditions : (*a*) A mixture of the nitrile (500 mg.), pyridine (10 ml.) and acetyl chloride (0·5 ml.) was refluxed for 6 hr. (*b*) A mixture of the nitrile (250 mg.), acetic anhydride (5 ml.), and acetyl chloride (0·5 ml.) was refluxed for 16 hr. The identity of each recovered nitrile with the starting material was proved by hydrolysis in the usual manner to the corresponding acid.

Addition of Hydrogen Cyanide to 3 : 4 : 5 : 6-*Tetrahydrobenzonitrile* (with K. Sams).—*cyclo*-Hexanone cyanohydrin was dehydrated with thionyl chloride in benzene (Ruzicka and Brugger, *Helv. Chim. Acta*, 1926, **9**, 399) to yield 3 : 4 : 5 : 6-tetrahydrobenzonitrile, b. p. 85—87°/18 mm., n_D^{19} 1·4821. Kidd, Robins, and Walker (*J.*, 1953, 3244) give b. p. 85—90°/17 mm., n_D^{19} 1·4864.

A solution of hydrogen cyanide was prepared by the addition of concentrated hydrochloric acid (20 ml.) to potassium cyanide (53 g.) in water (220 ml.), and was heated in a pressure bottle at 100° for 4 hr. with a solution of 3 : 4 : 5 : 6-tetrahydrobenzonitrile (22 g.) in ethanol (220 ml.). After removal of the alcohol, the aqueous solution was extracted with ether. The extract was washed with concentrated calcium chloride solution, dried ($CaCl_2$), and fractionated. A mixture of *cis*- and *trans*-hexahydrophthalonitrile was obtained, b. p. 184—188°/25 mm.; the distillate solidified almost completely, and after removal of oil on a porous tile melted at 42—46°.

No hexahydrophthalonitrile could be obtained by heating 3 : 4 : 5 : 6-tetrahydrobenzonitrile under reflux with liquid hydrogen cyanide and potassium cyanide as catalyst or by slow acidification of a boiling aqueous-ethanolic solution of the tetrahydronitrile and potassium cyanide.

cis-*Octahydro*-1-*imino*-3-*oxoisoindole.*—*cis*-2-Cyanohexahydrobenzamide (6·7 g.) was heated at 180—185° for 3 hr. The product was boiled with ethyl acetate, filtered off, and washed with ethyl acetate, to yield a brown solid (3·0 g.), m. p. 211—215° (decomp.). After crystallisation from 2-ethoxyethanol (charcoal), cis-*octahydro*-1-*imino*-3-*oxoisoindole* (VII) was obtained colourless and had m. p. 227—229° (decomp.) (Found : C, 62·95; H, 7·9; N, 18·3. $C_8H_{12}ON_2$ requires C, 63·1; H, 7·95; N, 18·4%). The *picrate*, crystallised from 2-ethoxyethanol–ethanol, had m. p. 204—206° (decomp.) (Found : C, 44·2; H, 4·15; N, 18·1. $C_{14}H_{15}O_8N_5$ requires C, 44·1; H, 4·0; N, 18·4%). The *hydrochloride*, crystallised from ethanol–ethyl acetate, had m. p. 201—203° (decomp.) (Found : C, 51·0; H, 7·0; N, 14·9; Cl, 18·9. $C_8H_{13}ON_2Cl$ requires C, 50·9; H, 6·9; N, 14·85; Cl, 18·8%). The free base (250 mg.) was boiled with water (4·0 ml.) for 3 hr., and the solution was cooled in ice; the precipitate (126 mg.) had m. p. 134—136°; evaporation of the filtrate gave a further crop (98 mg.) of the same m. p. Both crops had mixed m. p. 135—137° with *cis*-hexahydrophthalimide.

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The Dehydrochlorination of Isomeric Hexachlorocyclohexanes (Benzene Hexachlorides).

By P. O'Colla and (Miss) J. O'Sullivan.

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The mixtures obtained by the partial alkaline dehydrochlorination of four stereoisomeric hexachloro*cyclo*hexanes have been examined by chromatography on paper and on cellulose. In the dehydrochlorination of the α- and the β-isomer intermediate pentachloro- or tetrachloro-compounds were not detected, and this was in agreement with conclusions arrived at from kinetic studies by Hughes, Ingold, and Pasternak (*J.*, 1953, 3832). With the γ- and the δ-isomer, only pentachloro-intermediates accumulated and this too was consistent with the kinetic conclusions.

When the known isomers of hexachloro*cyclo*hexane (benzene hexachloride) are treated with an excess of alkali, each loses 3 moles of hydrogen chloride and forms a mixture of the three trichlorobenzenes. From kinetic and other evidence Hughes, Ingold, and Pasternak (*J.*, 1953, 3832) made deductions concerning the dehydrochlorination processes in each isomer. The chromatographic techniques developed for the analysis of chlorinated organic insecticides (Moynihan and O'Colla, *Chem. and Ind.*, 1951, 406; O'Colla, *J. Sci. Food Agric.*, 1952, 130) provided a sensitive method for the detection and isolation of any intermediate penta- or tetra-chloro-compounds in the reactions. Hence the products of the partial dehydrochlorination of four hexachloro*cyclo*hexane isomers were examined chromatographically to see if the results were in agreement with the deductions from kinetic data. Hughes *et al.* (*loc. cit.*) deduced that, for the α- and the β-isomer one, and for the γ- and the δ-isomer two rate-controlling steps were involved in the dehydrochlorination. Where two steps were involved the intervening pentachloro*cyclo*hexene was isolated, but they did not prove conclusively that other intermediate tetra- and penta-chloro-compounds were not present in smaller quantities.

In the present investigation the hexachloro*cyclo*hexanes were dehydrochlorinated in ethanol, by addition of known fractions of the theoretical quantity of sodium hydroxide required to bring about complete dehydrochlorination. Drops from the solution were examined by paper chromatography. When developed, sprayed, and heated, the chromatograms containing the products from the α- and the β-isomer each showed only one spot corresponding to the unchanged isomer. The methods used were capable of detecting 30—50 μg. of the possible intermediates. Spots containing up to 1 mg. of starting material were examined: hence no appreciable quantities of such intermediates were present. The chromatograms containing the products from the γ- and the δ-isomers showed two spots in each, corresponding to the unchanged isomers and the derived pentachloro*cyclo*hexenes. The three trichlorobenzenes were present in all cases, as shown later in column chromatography, but they were not detectable by the sprays used. These findings were confirmed by fractionation of the partially dehydrochlorinated β-, γ-, and δ-isomers on hydrocellulose columns, the same solvent system being employed as in the paper chromatography.

The column fractionation of the products from the β-isomer yielded only the unchanged isomer and three trichlorobenzenes. According to the hypothesis developed by Hughes *et al.* (*loc. cit.*) the pentachloro-intermediate from the β-isomer should be the same as that from the δ-isomer, and hence should be capable of isolation. However, it is evidently decomposed rapidly at the higher temperature necessary for the dehydrochlorination of the β-isomer. The column chromatography of the partially dehydrochlorinated γ- and δ-isomers yielded the intermediate pentachloro*cyclo*hexenes, together with the unchanged isomers and trichlorobenzenes. The chromatographically pure pentachloro-compound from the γ-isomer was a viscous liquid, whereas that from the δ-isomer had m. p. 69°. The latter compound also moved more slowly on a chromatogram, thus confirming previous evidence (*idem, loc. cit.*) that the compounds were quite different. In each fractionation the solvent was evaporated from the eluate fractions and residues were examined on paper chromato-

grams, since any hitherto undetected intermediates would be obtained in greater concentration by the procedure. No compound other than those already described was detected. Hence, the results obtained by the comparatively sensitive chromatographic examination were in agreement with the deductions from kinetic data concerning the elimination reactions.

In the course of the work it was found that the solvent system used by Ramsay and Patterson (*J. Assoc. Off. Agric. Chem.*, 1946, **29**, 337) for the separation of hexachloro*cyclo*hexanes on silicic acid columns also gave excellent separations when used on paper. The isomers separated in the same order as that obtained with the acetic anhydride–light petroleum system mainly used in the present investigation.

Experimental

The four hexachloro*cyclo*hexanes were kindly presented by Imperial Chemicals Limited. Examination by paper chromatography indicated traces of other isomers in each; *e.g.*, the γ- and the δ-isomer contained traces of α- and β-isomer, respectively. The isomers were purified by recrystallisation—the β-isomer from acetone and the others from chloroform. Two recrystallisations sufficed to produce chromatographically pure compounds.

Chromatographic Methods.—The paper chromatograms were prepared as described by O'Colla (*loc. cit.*). Acetic anhydride was the fixed phase with *n*-pentane, *n*-hexane, or light petroleum (b. p. 60—80°) as the mobile phase. When the solvent system devised by Ramsay *et al.* (*loc. cit.*) was used on filter-paper, this was impregnated with nitromethane, and *n*-hexane saturated with nitromethane was the mobile phase used. Hydrocellulose columns were prepared as previously described (O'Colla, *loc. cit.*), acetic anhydride being used as fixed phase with light petroleum (b. p. 60—80°) as mobile phase.

Location of Isomers.—The "visualiser" usually used was devised by Winteringham and Harrison (personal communication). The chromatograms were sprayed with monoethanolamine solution, heated to 100° for 30 min., and then sprayed with 1% silver nitrate solution containing nitric acid. When the strips were washed four times with distilled water and exposed to light, blue spots appeared. The limit of detection was 20 μg. of hexachloro*cyclo*hexane. The ferrous sulphate–acetic acid spray (O'Colla, *loc. cit.*) produced brown spots with any compound which was readily dehydrochlorinated, but it was necessary to heat the sprayed strips until the paper began to char. The limit of detection was 25 μg. of hexachloro- or 35 μg. of pentachloro-*cyclo*hexene.

Partial Dehydrochlorination of the Isomers.—Three solutions of each isomer were treated, respectively, with $\frac{1}{3}$, $\frac{1}{2}$, and $\frac{2}{3}$ of the quantity of alkali necessary for complete dehydrochlorination. The following preparation of one-third dehydrochlorinated α-, γ-, or δ-isomers is typical: The isomer (0·2 g.) in ethanol (5 ml.) was cooled to 0°, and sodium hydroxide (1·5 ml.; 0·5N) added during 30 min. After 24 hr. the neutral solution was concentrated to 2 ml. The dehydrochlorination of the β-isomer was conducted at 60°.

Paper Chromatography.—Drops from the 12 solutions were examined on paper chromatograms. When sprayed and heated after 16-hr. runs, the strips containing the products from the α- and the β-isomer showed only one spot corresponding to the unchanged isomer. The remaining chromatograms showed two spots in each, corresponding to the γ- and the δ-isomer and the pentachloro*cyclo*hexenes derived from them. The pentachloro-compound from the δ-isomer was prepared according to Cristol (*J. Amer. Chem. Soc.*, 1947, **69**, 338) and was chromatographically identical with that appearing on the δ-chromatograms. In a 16-hr. run, the distances in cm. moved by the detected compounds were: β- (25), δ- (31), γ-hexachloro*cyclo*hexene (40), δ- (43), α- (46), γ-pentachloro*cyclo*hexene (52).

Fractionation on Hydrocellulose Columns.—*γ-Isomer.* The γ-isomer (0·4 g.) was two-thirds dehydrochlorinated. The ethanolic solution was evaporated to dryness and the residue was extracted with light petroleum (b. p. 60—80°) saturated with acetic anhydride. The extract (10 ml.) was chromatographed on the column, and the eluate collected in fractions (15 ml.). Every fifth fraction was concentrated and examined on a paper chromatogram. The fractions which left residues when the solvent was evaporated were then amalgamated and examined as in the following Table.

δ-Isomer. The fractionation of the two-thirds dehydrochlorinated δ-isomer was similarly carried out, and the compounds isolated were δ-pentachloro*cyclo*hexene which, when recrystallised from light petroleum (b. p. 40—60°), had m. p. 69° (Found: Cl, 69·5%), unchanged δ-isomer, and a mixture of trichlorobenzenes.

Fractions	Description	Identified as		Cl, % : Found	Calc.
55— 90	Viscous liquid	$C_6H_3Cl_5$	B. p. 132°/12 mm.	69·5	69·7
130—150	Crystals	γ-Isomer	M. p. 113°	—	—
205—215	Crystals	1 : 3 : 5-Trichlorobenzene	M. p. 62°	58·3	58·7
215—220	Solid	Trichlorobenzene	M. p. 50—60°	57·8	—
220—240	Liquid	Mainly 1 : 2 : 4-trichlorobenzene	B. p. 214°/758 mm.	58·1	—

β-*Isomer.* A similar fractionation of two-thirds dehydrochlorinated β-isomer yielded only the unchanged β-isomer and a mixture of trichlorobenzenes. The β-isomer was found in fractions 180—190 of the eluate and the trichlorobenzenes were found in fractions 210—240.

The authors thank Professor C. K. Ingold, D.Sc., F.R.S., for directing their attention to this topic and for his interest and advice.

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The Equilibrium between Ethoxide and Hydroxide Ions in Ethanol and in Ethanol–Water Mixtures.

By E. F. CALDIN and G. LONG.

[Reprint Order No. 5225.]

The equilibrium constant for the reaction

$$OEt^- + H_2O \rightleftharpoons EtOH + OH^-$$

in ethanol–water at 25° has been determined. In mixtures containing a few per cent. of water, and in pure ethanol, the equilibrium favours ethoxide ion. It is deduced that solutions made by dissolving alkali hydroxides in ethanol will contain mainly ethoxide ion rather than hydroxide. For instance, in a 0·1M-solution of sodium hydroxide in 99% ethanol, 96% of the total base is ethoxide. Solutions made by dissolving sodium in ethanol or aqueous ethanol are also considered. The relative acid dissociation constants of ethanol and water, in (*a*) ethanol, and (*b*) water, are estimated; in each solvent they differ by less than a power of 10.

SEVERAL pieces of experimental evidence suggest that in pure ethanol, and in ethanol–water mixtures containing not more than a few per cent. of water by weight, the equilibrium

$$OEt^- + H_2O \rightleftharpoons OH^- + EtOH \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

lies in favour of the ethoxide ion. For example, the rate of the hydrolysis of an ester in ethanol–water to which hydroxide has been added becomes vanishingly small as the amount of water in the solvent approaches zero (Wegscheider and Ripper, *Sitzungsber. Akad. Wiss., Vienna,* **1918, 127,** II*b*, 129). This suggests that the concentration of hydroxide ion, which is the only ion present capable of hydrolysing the ester, approaches zero in solutions of low water content. Again, by infra-red spectroscopy, Williams and Bost (*J. Chem. Phys.*, **1936, 4,** 251) measured the amount of water produced when sodium hydroxide was dissolved in dry ethanol, and found that it corresponded to conversion of 75—100% of the hydroxide ion into ethoxide ion.

The thermodynamic equilibrium constant for reaction (1) in ethanol–water is given for any solvent composition by :

$$K = \frac{[OH^-]a_a}{[OEt^-]a_w} \cdot \frac{\gamma_{OH^-}}{\gamma_{OEt^-}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where the square brackets indicate molar concentrations; a_w and a_a are the activities of water and ethanol with respect to the pure liquids, and are known; and γ_{OEt^-} and γ_{OH^-} are the activity coefficients of ethoxide and hydroxide ions in any solvent mixture, the standard state being taken as the infinitely dilute solution in that solvent mixture. Since, however,

there are no data on $\gamma_{OH^-}/\gamma_{OEt^-}$, we must make use of the quantity K' defined by the equation:

$$K' = \frac{[OH^-]a_a}{[OEt^-]a_w} = K\frac{\gamma_{OEt^-}}{\gamma_{OH^-}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

K' is not a true thermodynamic constant, and its value will not be independent of the solvent composition, except at very low base concentrations.

It is convenient to define a third quantity, K°, by the following equation, in which $[H_2O]$ stands for the molar concentration of water:

$$K^\circ = [OH^-]/[OEt^-][H_2O] = K'a_w/a_a[H_2O] \quad . \quad . \quad . \quad . \quad (4)$$

This quantity is of interest in solutions of low water content. In such solutions, a_a is nearly unity, while the ratio $a_w/[H_2O]$ may be found from the Henry's law constant for dilute solutions of water in ethanol (from vapour pressure data in Landolt–Börnstein's "Tabellen," Springer, Berlin, 5th ed., 1931, Erg. II*b*, p. 1130), which gives $a_w = 0{\cdot}16\ [H_2O]$. Thus we find from (4) that K° in l. mole^{-1} is given in ethanol by:

$$K^\circ = 0{\cdot}16 \text{ (limiting value of } K' \text{ at low water concentration)} \quad . \quad . \quad (5)$$

It is possible to obtain an estimate of the magnitude of K°, and hence of K', in ethanol, from the data of Hine and Hine (*J. Amer. Chem. Soc.*, 1952, **74**, 5266) who measured the equilibrium constants for the reactions of *iso*propoxide ion with both hydroxide and ethoxide ions in *iso*propanol. The ratio of these constants gives the equilibrium constant for the reaction (1). The value obtained is $[OH^-][EtOH]/[OEt^-][H_2O] = 1{\cdot}27$. If we suppose that a change of solvent from *iso*propanol to ethanol does not alter the ratio of the activity coefficients of the ions, and if we put the concentration of EtOH in ethanol as 17 moles/l., this gives $K^\circ = 0{\cdot}074$ l./mole, and hence $K' = 0{\cdot}46$ in ethanol.

These results imply that when caustic alkali is added to ethanol the resulting solution contains much more ethoxide ion than hydroxide. This conclusion is of such general interest that an independent determination of K' is desirable. In the present investigation (of which a preliminary report was given in *Nature*, 1953, **172**, 583), the equilibrium constant K' has been measured at 25° in five ethanol–water mixtures containing from 12·6 to 47·0% of water by weight, by a colorimetric method; 2 : 4 : 6-trinitrotoluene was used as indicator, ionising in ethanol in the presence of a strong base to give a purple solution (Caldin and Long, to be published).

The equation used in the colorimetric determination of K' can be derived as follows. The coloured ion of trinitrotoluene is presumed to be produced by reaction with ethoxide or with hydroxide ion, and destroyed by reaction with ethanol or water. The reactions are (writing trinitrotoluene as BH)

$$BH + OEt^- \rightleftharpoons B^- + EtOH; \quad K_a = a_{B^-} \cdot a_a/a_{OEt^-} \cdot a_{BH} \quad . \quad . \quad (6)$$

$$BH + OH^- \rightleftharpoons B^- + H_2O; \quad K_w = a_{B^-} \cdot a_w/a_{OH^-} \cdot a_{BH} \quad . \quad . \quad (7)$$

Since we have no data on γ_{BH}, $\gamma_{B^-}/\gamma_{OEt^-}$, or $\gamma_{B^-}/\gamma_{OH^-}$, we must use, in place of K_a and K_w, quantities K_a' and K_w', defined as follows and not necessarily independent of composition:

$$K_a' = [B^-]a_a/[OEt^-][HB] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

and

$$K_w' = [B^-]a_w/[OH^-][HB] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

so that

$$K' = K_a'/K_w' \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

The total base concentration b, as found by titration with standard acid, is $b = [OH^-] + [OEt^-]$; the term $[B^-]$ is negligibly small. With equations (8) and (10), this relation gives:

$$[HB]/[B^-] = (a_a + a_wK')/bK_a' \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

Consideration of the rates of formation and destruction of the ion B^- gives the same equation.

The ratio $[HB]/[B^-]$ is related to the optical density, D, of the solution at a given wave-length. If e is the molar extinction coefficient of the ion B^-, l the length of the light-absorption path, and d the initial concentration of HB, then $[B^-] = D/el$ and $[HB] = d - D/el$. Substituting in equation (11), we find:

$$d/D = 1/el + (1/b)(a_a + a_wK')/elK_a' \quad . \quad . \quad . \quad . \quad . \quad (12)$$

Hence a plot of d/D against $1/b$ will be linear, with an intercept which gives us the extinction coefficient e of the coloured ion; and the ratio, R, of the intercept to the slope will be:

$$R = K_a'/(a_a + a_wK'), \text{ whence } K' = (K_a'/R - a_a)/a_w \quad . \quad . \quad . \quad (13)$$

From this expression K' has been determined as follows. Values of a_a and a_w were taken from vapour-pressure data as before. The value of R for each solvent mixture was obtained experimentally by measuring the optical density produced when a series of known volumes of base solution were added to a solution of trinitrotoluene contained in the reaction cell, about 8 measurements being made in each series. The base solutions were prepared by dissolving either sodium (for series 1 and 2) or sodium hydroxide (for series 3, 4, and 5) in the appropriate solvent mixture. The plot of d/D against $1/b$ was invariably linear within experimental error, and from the slope and intercept the ratio R could be determined within $\pm 5\%$. The value of K_a' is, as may be seen from equation (13), simply the value of R in pure ethanol, in which $a_w = 0$ and $a_a = 1$. If we assume as a first approximation that K_a' is a true constant, independent of solvent composition, we can use this value for all solvent mixtures. This approximation is considered below in the light of the results; it is the only approximation used in calculating K' from the observations. The experimental methods are described more fully in another paper (Caldin and Long, to be published) where also the value of K_a', obtained as described above, is reported as 2040 ± 70 l. mole^{-1} at 25°. It should perhaps be said that the evidence given in that paper does not exclude the possibility that the coloured species is a complex of trinitrotoluene with ethoxide ion, rather than an anion; if this were so, however, the mathematical treatment would be very similar, the numerical results would be of the same order, and our general conclusions would be unchanged.

TABLE 1. *Results at* 25·0°.

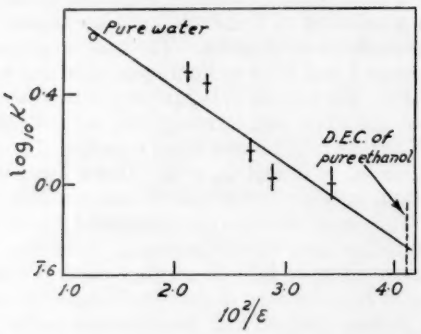
b = base concn. in mole l.$^{-1}$.
d = trinitrotoluene concn. (mean) in mole l.$^{-1}$.
e = extinction coefficient in mole^{-1} l. cm.$^{-1}$.
R in l. mole^{-1}.

Series no.	Wt. % of water	a_a	a_w	10^3d	Range of 10^3b	R	K'	$10^{-4}e$
1	12·6	0·762	0·516	1·1	0·19—2·84	1580	1·0 ± 0·2	1·30 ± 0·05
2	24·2	0·652	0·696	1·2	0·52—7·12	1470	1·1 ± 0·15	1·21 ± 0·05
3	28·8	0·623	0·734	1·1	0·39—6·68	1245	1·4 ± 0·2	1·22 ± 0·05
4	38·8	0·565	0·775	1·2	0·36—4·90	750	2·7 ± 0·3	1·27 ± 0·05
5	47·0	0·527	0·816	1·2	1·80—38·4	660	3·1 ± 0·3	1·24 ± 0·05

Table 1 summarises the experimental results, and the derived values of K', calculated by equation (13), and of the extinction coefficient e for the wave-length region used (about 0·5 μ). It will be seen that the extinction coefficient does not change appreciably with solvent composition; this confirms the assumption that the concentration measured optically is that of the same species throughout. The values for K' vary less than the ratio of water to ethanol in the solvent; they do however vary systematically with the solvent composition. This variation could be due either to variations in the ratio $\gamma_{OEt^-}/\gamma_{OH^-}$, which relates K' to the true thermodynamic constant K [equation (3)]; or to variations in $\gamma_{B^-}/\gamma_{OEt^-} \cdot \gamma_{HB}$, which relates K_a' (used in deriving K') to the true thermodynamic constant K_a [equations (6) and (8)]; or to both. That the former is the more important factor is indicated by the following evidence. The effect of added ethanol on

the rate, in water, of the hydrolysis of esters by hydroxides was studied by Scaife (Thesis, Leeds, 1938). His results agree with the assumption that only hydroxide ion can bring about the reaction, and the reduction in rate on adding ethanol is quantitatively accounted for if $K' = 4{\cdot}5$ in pure water. (It is unfortunately difficult to assess the accuracy of this estimate.) This value, which is independent of all values of K_a', is in agreement with the trend of the values of K' given in Table 1, as may be seen from the Figure in which $\log_{10} K'$ is plotted against the reciprocal of the dielectric constant (ε) of the solvent. This agreement supports the view that variations in $\gamma_{OEt^-}/\gamma_{HO^-}$ are the main source of the variations in K', rather than variations in K_a'. Thus our assumption that K_a' is to a first approximation independent of solvent composition seems to be justified.

A value of K' in pure ethanol may be obtained by extrapolation, from a plot of $\log_{10} K'$ against solvent composition, or against the reciprocal of the dielectric constant of the solvent mixture (Figure). We obtain, at 25°, $K' = 0{\cdot}5 \pm 0{\cdot}1$; whence $K^\circ = 0{\cdot}08 \pm 0{\cdot}02$ l. mole^{-1}. These values for the equilibrium constants in pure ethanol agree well with Hine and Hine's results in *iso*propanol. They are incidentally of the same order



Plot of $\log_{10}$ K′ *against reciprocal of dielectric constant* (ε) *of solvent mixture.*

of magnitude as those for the corresponding equilibrium in methanol, for which Unmack found $K' \simeq 1$ (*Z. physikal. Chem.*, 1928, **133**, 45, and earlier papers).

The Composition of "Alcoholic Hydroxide" Solutions.—When sodium hydroxide is dissolved in ethanol or an ethanol–water mixture, the resulting solution will contain hydroxide and ethoxide ions in equilibrium. The relative concentrations of the two ions can be calculated from the preceding results. Let the initial molar concentration of water be c; then the equilibrium concentration will, in virtue of equation (1), be $[H_2O] = c + [OEt^-]$. The total base concentration is $b = [OH^-] + [OEt^-]$. Combining these two equations with equation (4), we find $K^\circ = [OH^-]/(b - [OH^-])(c + b - [OH^-])$, whence by solving a quadratic we can find the fraction of base present as hydroxide, $[OH^-]/b$, in terms of b, c, and K°. The results for ethanol containing initially 0, 0·2, and 1·0% water by weight are given in Table 2. (Ethanol carefully treated to remove water

TABLE 2. *Percentage of total base present as hydroxide in solutions made by dissolving sodium hydroxide in ethanol and some ethanol–water mixtures, at* 25°.

	Total base (%) present as hydroxide at		
Wt. % of water in solvent	b = 0·1M	0·5M	1·0M
0	0·8	3·7	6·9
0·2	1·5	4·2	7·5
1·0	4·1	6·8	9·6

may contain 0·2% of water after a little handling in ordinary air.) We have used the value of $K^\circ = 0{\cdot}08$ l. mole^{-1} for pure ethanol, and have therefore confined our calculations to the range of base concentrations for which the final water concentration is not more than about 2% by weight. The effect of varying ionic strength on the ratio a_a/a_w has been neglected. It is clear from these figures that in such solutions most of the hydroxide added is converted into ethoxide. A similar conclusion will be true of methanol solutions. The

results refer to 25°, but are unlikely to be very different at temperatures up to the boiling point of ethanol.

The conclusion that when hydroxides are dissolved in ethanol (or methanol) the solution contains mainly ethoxide (or methoxide) rather than hydroxide ion throws light on several otherwise puzzling facts. (i) The addition of 1% of water has little effect on the rate or equilibrium of the reaction between ethoxide ion and trinitrotoluene or trinitrotriphenylmethane in ethanol (Caldin and Trickett, *Trans. Faraday Soc.*, 1953, **49**, 772; Caldin and Long, unpublished work). (ii) Baker and Neale (*Nature*, 1953, **172**, 583) observed nearly equal velocity constants for hydroxide and ethoxide in substitution and elimination reactions of benzyl nitrate in ethanol. (iii) In aromatic nucleophilic substitution reactions, use of "alcoholic hydroxide" solutions usually results in the introduction of an alkoxy- rather than a hydroxy-group. The rates of two such reactions—those of *o*-dinitrobenzene and of 1-chloro-2 : 4-dinitrobenzene—have been measured using hydroxide and ethoxide solutions, and in each case the two rates were very similar (Bunnett and Zahler, *Chem. Reviews*, 1951, **49**, 339, 340, 348). (iv) The conductances of solutions of sodium hydroxide and methoxide in methanol have similar values over a range of concentration, as have those of sodium hydroxide and ethoxide in ethanol; and the limiting conductances of the sodium hydroxide solutions are not abnormally large (Landolt–Börnstein, "Tabellen," Springer, Berlin, 5th edn., 1923, p. 1110; 1931, Erg. II*b*, p. 1068).

The Composition of Solutions made by Dissolving Sodium in Aqueous Alcohol.—The composition of solutions prepared by dissolving sodium in aqueous ethanol or "absolute alcohol" may be computed somewhat similarly. The amount of water removed from the solution according to reaction (1) is equivalent to the hydroxide produced, so that at equilibrium $[H_2O] = c - [OH^-]$. Hence $K^\circ = [OH^-]/(b - [OH^-])(c - [OH^-])$. This again gives us a quadratic from which $[OH^-]/b$ can be found in terms of b, c, and K°. The results for ethanol containing initially 0, 0·2, and 1·0% of water by weight are given in Table 3. We have again used the limiting value of K°, but the range of base concentrations to which this applies now extends to 10M. From the Table it is evident that nearly all the base is present as ethoxide.

TABLE 3. *Percentage of total base present as hydroxide in solutions made by dissolving sodium in ethanol–water mixtures, at* 25°.

Wt. % water in solvent	Total base (%) present as hydroxide at			
	b = 0·1M	0·5M	1·0M	10M
0	0·0	0·0	0·0	0·0
0·2	0·7	0·7	0·7	0·4
1·0	3·4	3·3	3·2	1·9

Because the equilibrium (1) is rapidly established, sodium will not remove water from ethanol to the same extent as from an inert solvent; the water will be largely regenerated. If more sodium is present, it will react with this water, and so on up to the limit set by the solubilities of sodium ethoxide and hydroxide; but there will always be an equilibrium concentration of water. The final concentration of water can be estimated; it is given (see the preceding paragraph) by $[H_2O] = c - [OH^-]$, where $[OH^-]$ at various total base concentrations can be found from Table 3. We estimate that to remove only half the water from ethanol containing either 0·2% or 1% of water by weight, it is necessary to raise the total base concentration above 10M, *i.e.*, to add more than 230 g. of sodium per litre (incidentally this treatment will remove about half the ethanol as ethoxide). These conclusions apply to 25°. They suggest that treatment with sodium at room temperature would be a relatively inefficient means of finally drying ethanol. The efficacy of magnesium ethoxide for this purpose is accounted for by the insolubility of magnesium hydroxide in ethanol; hydroxide ions formed by equilibrium (1) are removed from solution, the equilibrium is disturbed so that more water reacts with ethoxide, and the water is progressively removed.

Relative Acid Strengths of Ethanol and Water.—The equilibrium constant K, and hence to a good approximation K', is the ratio of the acid dissociation constant of water to that

of ethanol in any given solvent S, as may be seen by considering the equilibria $EtOH + S = SH^+ + OEt^-$ and $H_2O + S = SH^+ + OH^-$. In *ethanol*, we have found that K' at 25° is 0·5, so that the acid strengths of water and ethanol in this solvent are comparable, water being somewhat the weaker acid. In pure *water*, we find by extrapolation using the Figure that $\log_{10} K' = 0{\cdot}8\ (\pm 0{\cdot}3)$; so that the acid strengths are again not greatly different, water being about 5 times the stronger acid. These relatively small differences in acid strength between water and ethanol are in accord with the view (cf. Bell, "Acids and Bases," Methuen, London, 1952, chap. 3) that the differences, amounting to a factor of the order of 10^4, between the dissociation constants of neutral acids and bases measured in water and in ethanol can be attributed mainly to the differences in electrostatic forces, due to the difference of dielectric constant, rather than to a difference in the intrinsic acid strengths of the two solvents.

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Some Tautomeric Acridines.

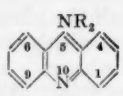
By R. M. ACHESON, M. L. BURSTALL, C. W. JEFFORD, and B. F. SANSOM.

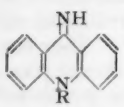
[Reprint Order No. 5271.]

Contrary to the conclusions reached by other workers using other methods, ultra-violet absorption measurements on solutions of 5-dimethylamino-, 5-imino-10-methyl-5 : 10-dihydro-, and 5-amino-acridine indicate that the last compound is largely present in the tautomeric form of 5-iminoacridan under the conditions of examination. Similar experiments indicate that acridone and thioacridone are present in solution in the CO and the CS form respectively.

THE question whether 5-aminoacridine is better represented as (I) or as (II), or as a tautomeric mixture, has been disputed. Attempts to decide it from chemical reactions have not been successful and could at best provide only negative evidence in favour of one formulation (cf. Angyal and Angyal, *J.*, 1952, 1461). Although physical methods are usually a better approach to questions of imine–amine tautomerism (cf. Angyal and Angyal, *loc. cit.*), dipole-moment determinations were inconclusive in this case (Short, *J.*, 1952, 4584; Pushkarev and Kokoshko, *Doklady Akad. Nauk S.S.S.R.*, 1953, **93**, 77). The similarity of the ultra-violet absorption spectra of 5-aminoacridine and 9-aminoanthracene led Craig and Short (*J.*, 1945, 419) to conclude that the imine form of the acridine played an insignificant part under the conditions of the examination. Similarly, the infra-red absorption spectra of 9-aminoanthracene, 5-aminoacridine, and various other amino-heterocycles were considered by Short (*loc. cit.*) to support the thesis that 9-aminoanthracene

(I; R = H)
(III; R = Me)





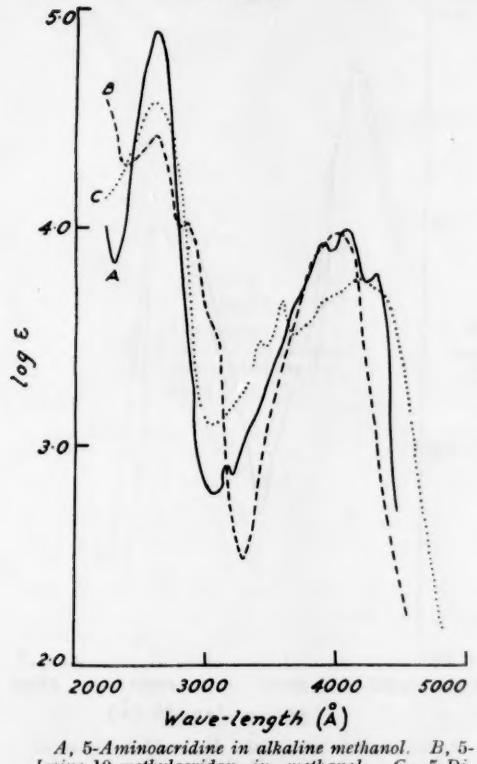
(II; R = H)
(IV; R = Me)

was best represented as such, rather than as anthrone imine, and to confirm his earlier view that 5-aminoacridine did not contain appreciable quantities of the imine form under the conditions of the examination; however, Karyakin, Grigorovskii, and Yaroslavskii (*Doklady Akad. Nauk S.S.S.R.*, 1949, **67**, 679) came to the opposite conclusion, after

examination of the infra-red absorption spectra of a number of compounds in the 1—2-μ region.

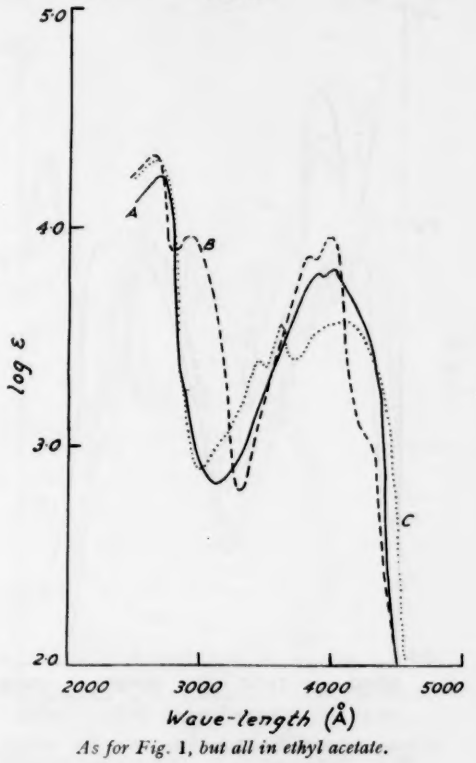
It appeared to us that the similarity between the ultra-violet absorption spectra of 5-aminoacridine and 9-aminoanthracene was insufficiently close to warrant definite structural conclusions, while the similarity of the spectrum of 5-aminoacridine with that of acridone, but not with those of 1-, 2-, 3-, and 4-aminoacridine (Craig and Short, *loc. cit.*), appeared significant. The observations by King, Gilchrist, and Tarnoky (*Biochem. J.*, 1946, **40**, 706) that the ultra-violet absorption spectra of 2-chloro-5-diacetylaminoacridine,

FIG. 1.



A, 5-Aminoacridine in alkaline methanol. B, 5-Imino-10-methylacridan in methanol. C, 5-Dimethylaminoacridine in methanol.

FIG. 2.



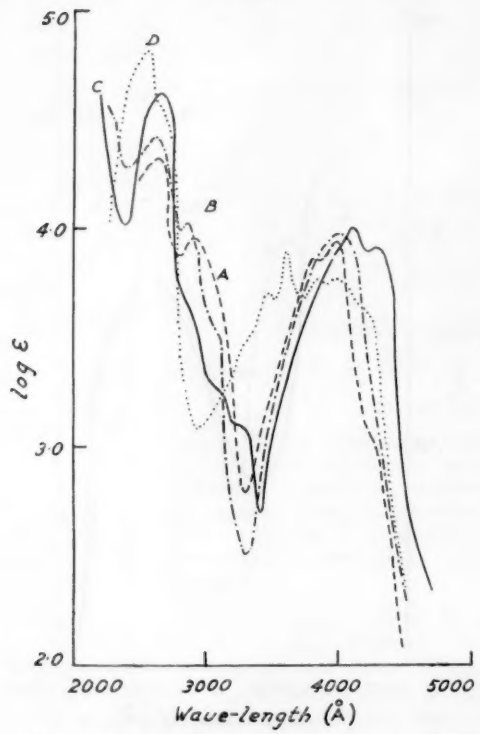
As for Fig. 1, but all in ethyl acetate.

the structure of which was proved by analogy (Wilkinson and Finar, *J.*, 1946, 115), in neutral and acid solution were very similar to those of acridine but dissimilar from those of 5-aminoacridine under the same conditions suggested, although inconclusively, that the latter compound had the imine structure. The absorption spectrum of 5-aminoacridine (I and/or II) was therefore compared (Figs. 1 and 2) with those of 5-imino-10-methylacridan (IV) and 5-dimethylaminoacridine (III), which cannot tautomerise, in methanol and ethyl acetate solution [only 5-dimethylaminoacridine was sufficiently soluble in *cyclo*hexane (Fig. 3)]. While the spectra of 5-aminoacridine and the imino-compound (IV) have much in common, that of 5-dimethylaminoacridine (III) is quite different and is remarkably similar to those of 1-, 2-, 3-, and 4-aminoacridines which also exhibit maxima at 3450 and 3600 Å, and have broad bands in the 4000-Å region. The latter comparison indicates that 5-dimethylaminoacridine can be used as a fair spectral model for the amine form. It therefore appears that the unmethylated compound is probably very largely present as the

imine under the conditions of examination. If much of the amine form were present inflexions or maxima would be expected at *ca.* 3400 and 3600 Å as in the case of 5-dimethylaminoacridine. It is interesting that similar methods applied to 2- and 4-aminopyridine have shown that the imino-forms can be present in, at most, very small proportion (Anderson and Seeger, *J. Amer. Chem. Soc.*, 1949, **71**, 340).

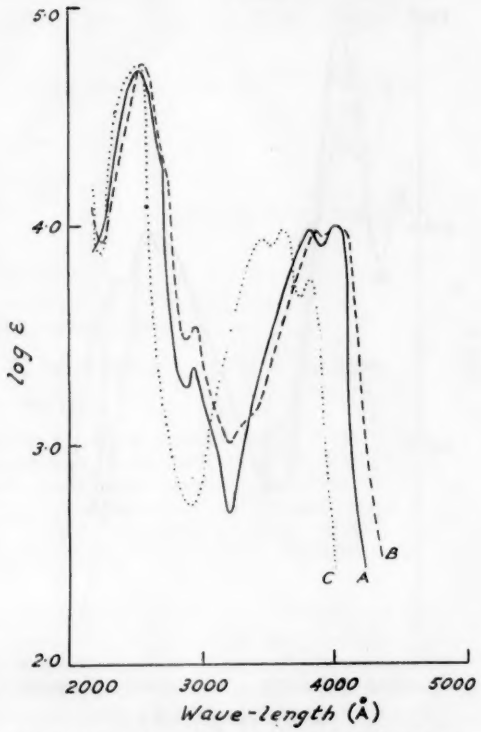
Infra-red absorption spectra of these three acridines (in paraffin pastes) in the carbonyl region appear superficially neither to confirm nor to discredit this conclusion which

FIG. 3.



5-Imino-10-methylacridan, (A) in ethyl acetate, (B) in alkaline methanol. C, 5-Amino-10-methylacridinium iodide in methanol. D, 5-Dimethylaminoacridine in cyclo*hexane.*

FIG. 4.



A, Acridone in methanol. B, 10-Methylacridone in methanol. C, 5-Methoxyacridine in cyclo*hexane.*

receives some support from their fluorescences (see Table). Attempts to measure the infra-red absorption spectrum of 5-aminoacridine and 5-imino-10-methylacridan in chloroform in the 3-μ region failed because of their low solubility. The solid iminoacridan

	Fluorescence in aqueous ethanol		
Acridine	Alkaline	Neutral	Acid
5-Aminoacridine (I or II)	Intense green	Green	Blue
5-Imino-10-methylacridan (IV)	Weak blue-green	Blue-green	Blue-green
5-Dimethylaminoacridine (III)	None	None	None

showed two very small maxima in this region in paraffin paste, in contrast to the one which would be expected by analogy with Angyal and Werner's observations (*J.*, 1952, 2911) on the dihydroiminopyridines. For 5-aminoacridine two maxima were found. From this it

might be inferred that the amino-form was present in the solid lattice but such a conclusion requires much further substantiation in view of the likelihood of "mesohydric tautomerism" (cf. Hunter, *J.*, 1945, 806) under these conditions.

The expression used by Angyal and Angyal (*loc. cit.*) to determine the equilibrium constants of the amine–imine system in the pyridine series can be applied to the acridine problem. The approximate pK_a values available (Albert and Goldacre, *J.*, 1943, 454; 1946, 706) for 5-amino-10-methylacridinium bromide and 5-aminoacridine suggest that both the amine and the imine of the latter have the same order of stability. (Incidentally this approach confirms conclusions drawn from optical data in the pyridine series.)

There is also a great similarity between the spectra of 10-methylacridone (Fig. 4) and

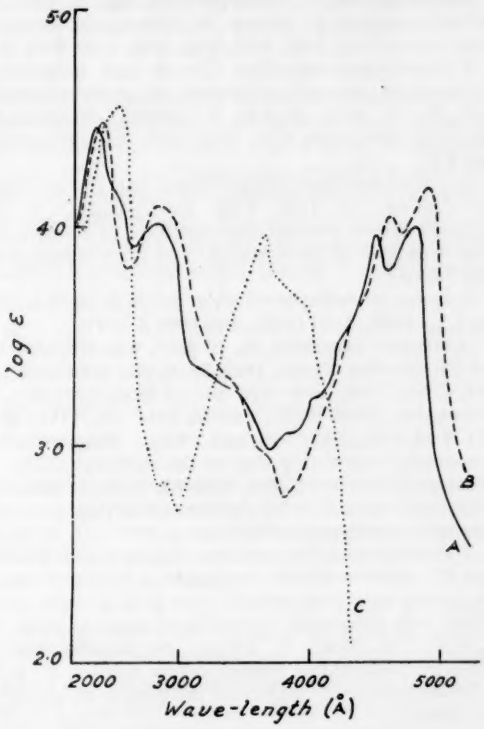


FIG. 5.
A, Thioacridone.
B, 10-Methyl(thioacridone).
C, 5-(Methylthio)acridine.
All in methanol.

5-imino-10-methylacridan (Fig. 3). The spectra of the latter compound in ethyl acetate and methanol solutions are similar (Fig. 3), the second being identical with that of 5-amino-10-methylacridinium iodide in methanolic potassium hydroxide. This suggests that dehydration of the acridinium hydroxide first formed is rapid, and provides no evidence for the formation of the intermediate acridan as postulated by Albert and Ritchie (*J.*, 1943, 458); the "acridan" precipitated by aqueous sodium hydroxide from 5-amino-10-methylacridinium salts is presumably the imine hydrate. Acridan itself has a structureless maximum at 2900 Å (Blout and Corley, *J. Amer. Chem. Soc.*, 1947, **69**, 763) falling slowly with decrease in wave-length, as is found with other acridans (Tarnoky, *Biochem. J.*, 1950, **46**, 297).

Similarly a comparison of the ultra-violet absorption spectra of acridone, 10-methylacridone, and 5-methoxyacridine (Fig. 4) shows that acridone is much better represented as such rather than as 5-hydroxyacridine. Similar conclusions regarding the structure of thioacridone can be drawn from the data on Fig. 5. It is of interest that 5-methoxy-

acridine crystallises from aqueous solvents as the hydrate, which is claimed (Drozdov and Cherntsov, *J. Gen. Chem., U.S.S.R.*, 1944, **14**, 181; cf. Barber, Wilkinson, and Edwards, *J. Soc. Chem. Ind.*, 1947, **66**, 411) to react much more readily than the anhydrous compound with hydrogen cyanide to give 5-cyanoacridine; this led to the supposition that the hydrate was best represented as 5-hydroxy-5-methoxyacridan. As the ultra-violet absorption spectra of anhydrous 5-methoxyacridine in *cyclo*hexane and of the hydrate in aqueous methanol are very similar and differ very much from those of acridans this suggestion can no longer be upheld.

Experimental

Aminoacridines.—5-Aminoacridine, m. p. 234°, was prepared from 5-methoxyacridine hydrate according to Barber, Wilkinson, and Edwards (*loc. cit.*). In paraffin paste infra-red max. were at 2·88, 3·04, 6·02, 6·04, 6·19, 6·40, 6·45, 6·59, 6·73, 6·86, 7·15, 7·30, and 7·90 μ.

5-Dimethylaminoacridine (Dupré and Robinson, *J.*, 1945, 529) separated from light petroleum in pale yellow rhombs, m. p. 60° (Found: C, 81·0; H, 6·3; N, 12·0. Calc. for $C_{15}H_{14}N_2$: C, 81·2; H, 6·3; N, 12·5%). In paraffin paste infra-red max. were at 6·15, 6·20, 6·42, 6·50, 6·60, 6·66, 6·82, 6·92, 7·00, 7·10, 7·21, 7·28, and 7·98 μ. There was no maximum near 3 μ.

5-Imino-10-methylacridan (Albert and Ritchie, *loc. cit.*) was a pale brown friable solid, m. p. 134° (Found: N, 13·4. Calc. for $C_{14}H_{12}N_2$: N, 13·5%). Attempted crystallisation from methanol caused gradual decomposition to 10-methylacridone. In paraffin paste the infra-red max. were at 3·02 (very small), 3·08 (very small), 5·98, 6·24, 6·28, 6·46, 6·71, 6·83, 7·32, 7·42, 7·76, 7·90 μ.

5-Amino-10-methylacridinium iodide in methanolic potassium hydroxide showed $\lambda_{max.}$ 2625 (log $\varepsilon_{max.}$ 4·42), 2850 (4·22), and 4000 Å (3·97).

Acridones.—Acridone, m. p. 350°, was prepared from 9-chloroacridine according to Albert and Ritchie (*Org. Synth.*, 1942, **22**, 5) and in paraffin paste showed max. at 6·11, 6·26, 6·43, 6·54, 6·87, 7·28, 7·45, and 7·95 μ. 10-Methylacridone, m. p. 203—204° (Eckert and Steiner (*Sitzungsber. Akad. Wiss., Vienna*, 1914, IIb, 1141), in paraffin paste showed max. at 6·13, 6·26, 6·71, 6·84, 7·31, 7·47, 7·76, and 7·89 μ. The absorption max. at 6·11 and 6·13 in the last two compounds is probably due to the carbonyl group. 5-Methoxyacridine hydrate, m. p. 103° (decomp.) (Lehmstedt, *Ber.*, 1935, **68**, 1455), in methanol showed $\lambda_{max.}$ 2450 (log $\varepsilon_{max.}$ 4·77), 3560 (4·03), and 3700 Å (3·87); prolonged drying over phosphoric oxide *in vacuo* at 60° yielded anhydrous 5-methoxyacridine, m. p. 65°.

Thioacridones.—Thioacridone (Edinger and Arnold, *J. pr. Chem.*, 1901, **64**, 196) separated from 2% aqueous sodium hydroxide or from methanol in red needles, m. p. 265—267°, which in the former case were ground with boiling water to remove sodium hydroxide (Found, after drying over potassium hydroxide *in vacuo* at room temperature: C, 74·1; H, 4·4. Calc. for $C_{13}H_9NS$: C, 73·9; H, 4·3%). No monohydrate was obtained (cf. Edinger and Arnold). 5-(Methylthio)acridine formed yellow needles, m. p. 113—114° (Edinger and Arnold, *loc. cit.*). 10-Methyl(thioacridone) formed red needles m. p. 263° (cf. Gleu and Schaarschmidt, *Ber.*, 1939, **72**, 1249).

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Oxford University. [*Received, April 1st*, 1954.]

Addition of Free Radicals to Unsaturated Systems. Part X. The Reaction of Hydrogen Bromide with Tetrafluoroethylene and Chlorotrifluoroethylene.*

By R. N. Haszeldine and B. R. Steele.

[Reprint Order No. 5405.]

The photochemical reaction of hydrogen bromide with tetrafluoroethylene yields $H{\cdot}[C_2F_4]_n{\cdot}Br$, where $n = 1, 2, 3$, etc. Chlorotrifluoroethylene similarly yields $H{\cdot}[CFCl{\cdot}CF_2]_n{\cdot}Br$ and the bromine atom thus attacks the CF_2 group of the olefin; poly(chlorotrifluoroethylene) is formed by head-to-tail addition. The mechanisms of the reactions and in particular the fate of the hydrogen atoms are discussed.

That hydrogen bromide can react with olefins by mechanisms involving either electrophilic attack or attack by a bromine atom is now well established. An unsubstituted olefin is particularly susceptible to electrophilic attack, however, and it is thus difficult to suppress the reaction involving ionic intermediates even under conditions which strongly favour the radical mechanism. Unsubstituted olefins do not polymerise readily under the conditions normally used for their reaction with hydrogen bromide under free-radical conditions, and the chain-propagation reaction in the sequence below has never been reported when R or R′ = alkyl, aryl, etc. Such a propagation reaction would clearly provide strong support for a free-radical mechanism.

$$HBr \longrightarrow H\cdot + Br\cdot$$

$$Br\cdot + CR_2{:}CR'_2 \longrightarrow CR_2Br{\cdot}CR'_2\cdot \quad \text{Initiation}$$

$$CR_2Br{\cdot}CR'_2\cdot + CR_2{:}CR'_2 \longrightarrow CR_2Br{\cdot}CR'_2{\cdot}CR_2{\cdot}CR'_2\cdot \text{ etc.} \quad \text{Propagation}$$

$$CR_2Br{\cdot}CR'_2\cdot + HBr \longrightarrow CR_2Br{\cdot}CHR'_2 + Br\cdot \longrightarrow \text{etc.} \quad \text{Transfer}$$

Polyhalogeno-olefins resist electrophilic attack yet, as pointed out in earlier papers, are still sensitive to free-radical attack. By use of polyhalogeno-olefins, and in particular of polyfluoro-olefins, it should thus be possible to observe two effects during photochemical reaction with hydrogen bromide: (*a*) the free-radical reaction to the complete exclusion of the ionic reaction, and (*b*) the polymerisation of the fluoro-olefin.

Hydrogen bromide and tetrafluoroethylene (R = R′ = F) do not react at room temperature in absence of light, but readily combine when exposed to light of wavelength > 3000 Å (Pyrex vessels). When approximately equimolar quantities are used the product is almost completely 1-bromo-1 : 1 : 2 : 2-tetrafluoroethane and only traces of products with a higher boiling point are formed, thus revealing the efficiency of the chain-transfer step relative to the propagation step. It is noteworthy that molecular hydrogen, even in traces, is not produced during the photochemical reaction, thus showing either that the reaction chain is very long so that only infinitesimal amounts of hydrogen are produced, or that the hydrogen atom produced by the photolysis of a molecule of hydrogen bromide in the initial step combines with the olefin in some way, probably by initial formation of the dihydro-olefin and generation of a bromine atom:

$$H\cdot + CF_2{:}CF_2 \longrightarrow CHF_2{\cdot}CF_2\cdot$$

$$CHF_2{\cdot}CF_2\cdot + HBr \longrightarrow CHF_2{\cdot}CHF_2 + Br\cdot$$

This is followed by the usual chain reaction

$$Br\cdot + CF_2{:}CF_2 \longrightarrow CF_2Br{\cdot}CF_2\cdot$$

$$CF_2Br{\cdot}CF_2\cdot + HBr \longrightarrow CF_2Br{\cdot}CHF_2 + Br\cdot \longrightarrow \text{etc.}$$

* Part IX, Haszeldine, Leedham, and Steele, *J.*, 1954, 2040.

The fate of the hydrogen atom in the mechanism proposed for the photochemical reaction of hydrogen bromide with olefins has hitherto been ignored. The above suggestion is not implausible, since there is no reason to assume that the hydrogen atom is unreactive and incapable of attacking the double bond of tetrafluoroethylene, or that the $CHF_2{\cdot}CF_2$ radical should fail to abstract hydrogen from hydrogen bromide in a manner similar to the $CF_2Br{\cdot}CF_2$ radical. It is evident that if the reaction chain is long, the actual amount of 1 : 1 : 2 : 2-tetrafluoroethane produced is extremely small, and the fact that this compound could not be detected in the reaction products suggests that the reaction chain is long; experiments on a larger scale might render its spectroscopic detection possible.

A simple mechanism similar to that postulated above to explain the fate of the hydrogen atom can be applied to the reactions involving the photochemical reaction of bromotrichloromethane with olefins. In these reactions the fate of the bromine atom produced in the step

$$CCl_3Br \xrightarrow{h\nu} CCl_3{\cdot} + Br{\cdot}$$

has always been ignored, and it has somewhat arbitrarily been concluded that the CCl_3 radical initiates all the reaction chains :

$$CCl_3{\cdot} + CR_2{:}CR'_2 \longrightarrow CCl_3{\cdot}CR_2{\cdot}CR'_2{\cdot} \xrightarrow{CCl_3Br} CCl_3{\cdot}CR_2{\cdot}CR'_2Br + CCl_3{\cdot} \longrightarrow \text{etc.}$$

There is no reason why a bromine atom produced by photolysis of bromotrichloromethane should not attack the olefin in the same manner as a bromine atom produced from hydrogen bromide; after the first step, however, a CCl_3 radical will be generated :

$$Br{\cdot} + CR_2{:}CR'_2 \longrightarrow CR_2Br{\cdot}CR'_2{\cdot}$$

$$CR_2Br{\cdot}CR'_2{\cdot} + CCl_3Br \longrightarrow Cr_2Br{\cdot}CR'_2Br + CCl_3{\cdot}$$

followed by the chain reaction

$$CCl_3{\cdot} + CR_2{:}CR'_2 \longrightarrow CCl_3{\cdot}CR_2{\cdot}CR'_2{\cdot} \xrightarrow{CCl_3Br} CCl_3{\cdot}CR_2{\cdot}CR'_2Br + CCl_3{\cdot} \longrightarrow \text{etc.}$$

so that both the CCl_3 radical and the bromine atom from the initial photochemical fission of bromotrichloromethane can be considered to initiate chain reactions in which the CCl_3 radical is the chain carrier.

Irradiation of tetrafluoroethylene and hydrogen bromide in a molar ratio *ca.* 10 : 1 enables compounds of the type $H{\cdot}[CF_2{\cdot}CF_2]_n{\cdot}Br$ to be isolated, where $n = 1, 2, 3$, etc. The $CF_2Br{\cdot}CF_2$ radical formed initially can react with tetrafluoroethylene to propagate the chain, or with hydrogen bromide to undergo chain transfer. Despite the high concentration of tetrafluoroethylene, which is known to polymerise extremely rapidly by a free-radical mechanism, the yields of products where $n = 1$, 2, and 3 are 66, 12, and 0·5% respectively; this again illustrates the extreme efficiency of chain-transfer reactions involving hydrogen bromide. In all other free-radical reactions involving tetrafluoroethylene the difficulty is to suppress the propagation reaction in favour of the transfer reaction (see, *e.g.*, *J.*, 1953, 3761).

The compounds where $n = 2$, 3, etc., are not produced by reactions of the type

$$CHF_2{\cdot}CF_2Br \xrightarrow{h\nu} CHF_2{\cdot}CF_2{\cdot} \xrightarrow{C_2F_4} CHF_2{\cdot}CF_2{\cdot}CF_2{\cdot}CF_2{\cdot}$$

$$CHF_2{\cdot}CF_2{\cdot}CF_2{\cdot}CF_2{\cdot} \xrightarrow{CHF_2{\cdot}CF_2Br} H{\cdot}[CF_2{\cdot}CF_2]_2{\cdot}Br + CHF_2{\cdot}CF_2{\cdot}$$

since the C–Br bond in 1-bromo-1 : 1 : 2 : 2-tetrafluoroethane is not split homolytically by light of the wave-length used.

The reaction of hydrogen bromide with chlorotrifluoroethylene was studied by Park, Sharrah, and Lacher (*J. Amer. Chem. Soc.*, 1949, **71**, 2339), but since a charcoal catalyst was used it cannot be decided whether ionic or radical intermediates were involved in the formation of the 1-bromo-2-chloro-1 : 1 : 2-trifluoroethane isolated. The present study has shown that in absence of a catalyst there is no reaction in the dark, *i.e.*, electrophilic

attack is very slow, but that ready reaction occurs on exposure to light. In Pyrex vessels only 1-bromo-2-chloro-1 : 1 : 2-trifluoroethane (I) is produced. That the product has the constitution (I) is shown by its dehalogenation to give trifluoroethylene in high yield. The other possible product of formula $H{\cdot}[C_2ClF_3]{\cdot}Br$ which might be produced by the photochemical reaction is (II). This could not yield trifluoroethylene when treated with

$CF_2Br{\cdot}CHFCl$ (I) $\qquad$ $CHF_2{\cdot}CFClBr$ (II) $\qquad$ $CF_2Br{\cdot}CFCl{\cdot}CF_2{\cdot}CHFCl$ (III)

zinc and ethanol, but would yield 1-chloro-1 : 2-difluoroethylene, or, if reduction occurred initially, would give 1 : 2-difluoroethylene :

$$CHF{:}CFCl \longleftarrow CHF_2{\cdot}CFClBr \longrightarrow CHF_2{\cdot}CHFCl \longrightarrow CHF{:}CHF$$

The absence of these olefins and the high yield of trifluoroethylene strongly suggest that the product $H{\cdot}[C_2ClF_3]{\cdot}Br$ is exclusively (I). Bromine atom attack is thus on the CF_2 group of chlorotrifluoroethylene :

$$Br{\cdot} + CF_2{:}CFCl \longrightarrow CF_2Br{\cdot}CFCl{\cdot}$$
$$CF_2Br{\cdot}CFCl{\cdot} + HBr \longrightarrow CF_2Br{\cdot}CHFCl + Br{\cdot} \longrightarrow \text{etc.}$$

Despite claims to the contrary (Henne and Kraus, *J. Amer. Chem. Soc.*, 1951, **73**, 1791; see, however, *idem*, *ibid.*, 1954, **76**, 1175) it was earlier conclusively demonstrated that attack of a trifluoromethyl radical derived from trifluoroiodomethane was exclusively on the CF_2 group of chlorotrifluoroethylene (Haszeldine and Steele, *J.*, 1953, 1592). The result obtained with hydrogen bromide thus independently establishes the direction of radical addition to chlorotrifluoroethylene and shows that, as expected, a bromine atom and a trifluoromethyl radical behave in a similar manner.

Irradiation of an approximately equimolar mixture of hydrogen bromide and chlorotrifluoroethylene in silica vessels initiates a fast reaction, and the product is again mainly (I). The use of light of shorter wave-length doubtless activates the olefin to a certain extent and also gives a more energetic bromine atom, and chain propagation therefore occurs to a small extent. Chain propagation is substantially increased when the molar ratio of chlorotrifluoroethylene to hydrogen bromide is *ca.* 6 : 1 but, as with the tetrafluoroethylene reaction, the chain-transfer step is very efficient :

$$Br{\cdot} + CF_2{:}CFCl \longrightarrow CF_2Br{\cdot}CFCl{\cdot} \xrightarrow{CF_2{:}CFCl} CF_2Br{\cdot}CFCl{\cdot}[C_2ClF_3]_m{\cdot}$$
$$CF_2Br{\cdot}CFCl{\cdot}[C_2ClF_3]_m{\cdot} \xrightarrow{HBr} CF_2Br{\cdot}CFCl{\cdot}[C_2ClF_3]_m{\cdot}H + Br{\cdot} \longrightarrow \text{etc.}$$

and the polymer isolated is of short chain length ($m = 1, 2, 3$, etc.). That the compound where $m = 1$ is 1-bromo-2 : 4-dichloro-1 : 1 : 2 : 3 : 3 : 4-hexafluorobutane (III) is shown by its reaction with zinc and dioxan to give a high yield of 4-chloro-1 : 1 : 2 : 3 : 3 : 4-hexafluorobut-1-ene (IV). The infra-red spectrum of this compound shows a C:C stretching vibration at 5·56 μ, the position shown (Haszeldine, *J.*, 1952, 4423) to be characteristic of compounds which contain the $\cdot CF{:}CF_2$ group.

$CF_2{:}CF{\cdot}CF_2{\cdot}CHFCl$ (IV) $\qquad$ $CF_2Br{\cdot}CFCl{\cdot}CF_2{\cdot}CFCl{\cdot}CF_2{\cdot}CHFCl$ (V)

The compound where $m = 2$, and material of average composition $m = 5$, have infra-red spectra very similar to that of (III) and to those of the compounds $CF_3{\cdot}[CF_2{\cdot}CFCl]_n{\cdot}I$ described earlier (*J.*, 1953, 1592). The compound where $m = 2$ thus very probably has constitution (V), and the polychlorotrifluoroethylene chain is built up by head-to-tail addition with radical attack throughout on the CF_2 group of the olefin to give $Br{\cdot}[CF_2{\cdot}CFCl]_n{\cdot}H$.

The infra-red spectrum of the 1-bromo-2-chloro-1 : 1 : 2-trifluoroethane isolated from the photochemical experiments shows significant differences from that of the material

isolated by Park *et al.* (see p. 3751), and the thermal reaction of hydrogen bromide with chlorotrifluoroethylene in presence of a charcoal catalyst was therefore studied. Only 1-bromo-2-chloro-1 : 1 : 2-trifluoroethane was isolated, and its spectrum was identical with that of the photochemical product. It should be noted that the reaction of chlorotrifluoroethylene with a hydrogen halide, HX, by a reaction involving ionic intermediates, would yield $CF_2X{\cdot}CHFCl$, *i.e.*, both the free-radical and the ionic-type reaction of hydrogen bromide with chlorotrifluoroethylene yield the same product; only the free-radical reaction can yield polymeric products, however.

Experimental

Hydrogen bromide, prepared by Duncan's method (*Inorg. Synth.*, **1**, 151) was freed from traces of bromine, dried (P_2O_5), and carefully purified by fractionation *in vacuo* (Found: *M*, 81·0; Calc. for HBr: *M*, 81·0). Chlorotrifluoroethylene (Found: *M*, 116·5. Calc. for C_2ClF_3: *M*, 116·5) and tetrafluoroethylene (Found: *M*, 100. Calc. for C_2F_4: *M*, 100) were commercial samples, purified by repeated distillation, and shown by infra-red spectroscopic examination to be free from impurities. Irradation experiments were carried out in sealed Pyrex or silica tubes, with rigid exclusion of air, moisture, etc. A Hanovia lamp was used without the Wood's filter as a source of ultra-violet radiation. Liquid products were distilled through specially designed columns which have a minimum hold-up. Hydrogen was not formed during the photochemical reactions described below; its presence in even small amount would have been readily detected by the sensitive vacuum techniques used.

Reaction of Hydrogen Bromide with Tetrafluoroethylene.—The olefin and hydrogen bromide did not react when kept for 14 days in a sealed tube in the dark. Tetrafluoroethylene (8·50 g., 0·085 mole) and hydrogen bromide (0·76 g., 0·0094 mole) were sealed in a Pyrex vessel (300 ml.) and irradiated for 2 days. A small amount of solid polymer was formed on the side of the tube. The unchanged olefin was separated from the reaction products and was resealed with hydrogen bromide (0·95 g.) and again irradiated (2 days). The unchanged olefin was combined with fresh tetrafluoroethylene (2·5 g.) and hydrogen bromide (0·75 g.) and exposed to light again (2 days). The combined products (from 11·00 g., 0·11 mole, of C_2F_4, and 2·46 g., 0·03 mole, of HBr) were distilled to give unchanged tetrafluoroethylene (7·00 g., 64%) and liquid products (5·25 g.). These were distilled to give 1-bromo-1 : 1 : 2 : 2-tetrafluoroethane (3·64 g., 66% based on hydrogen bromide), b. p. 12·5° (Found: C, 13·6; H, 0·7%; *M*, 182. Calc. for C_2HBrF_4: C, 13·3; H, 0·6%; *M*, 181), *1-bromo-1 : 1 : 2 : 2 : 3 : 3 : 4 : 4-octafluorobutane* (1·0 g., 12%), b. p. 66°, n_D^{20} 1·309 (Found: C, 16·8; H, 0·7%; *M*, 280. C_4HBrF_8 requires C, 17·1; H, 0·4%; *M*, 281), and a residual fraction of *1-bromo-1 : 1 : 2 : 2 : 3 : 3 : 4 : 4 : 5 : 5 : 6 : 6-dodecafluorohexane* (0·3 g., 0·5%) (Found: C, 18·8; H, 0·4. C_6HBrF_{12} requires C, 18·9; H, 0·3. Calc. for C_6HBrF_{16}: C, 20·0%). Park *et al.* (*loc. cit.*) report b. p. −3·5°/626 mm. for 1-bromo-1 : 1 : 2 : 2-tetrafluoroethane.

Reaction of Hydrogen Bromide with Chlorotrifluoroethylene.—(a) *In the dark.* There was no reaction when hydrogen bromide (6·5 g., 0·080 mole) and chlorotrifluoroethylene (9·4 g., 0·082 mole) were sealed in a 300-ml. Pyrex vessel and kept in the dark for 3 days.

(b) *In Pyrex vessels.* When the reaction mixture of (a) was exposed to ultra-violet light, an immediate reaction was observed and gave, after 2 days, unchanged reactants (1·2 g.) (*M*, 100) and 1-bromo-2-chloro-1 : 1 : 2-trifluoroethane (14·7 g., 93% conversion), b. p. 52·5°, n_D^{20} 1·3705, n_D^{25} 1·368 (Found: C, 12·1; H, 0·7%; *M*, 197·5. Calc. for $C_2HBrClF_3$: C, 12·1; H, 0·5%; *M*, 197·5). Park *et al.* (*loc. cit.*) report b. p. 46·02°/615 mm., n_D^{25} 1·3685.

(c) *In silica vessels.* Hydrogen bromide (2·9 g., 0·036 mole) and chlorotrifluoroethylene (3·1 g., 0·027 mole), sealed in a silica tube and irradiated for 2 hr., gave unchanged hydrogen bromide (0·7 g., 24%) (Found: *M*, 81) and 1-bromo-2-chloro-1 : 1 : 2-trifluoroethane (4·5 g., 88%), b. p. 52·5—53°, n_D^{20} 1·371, shown by infra-red spectroscopic examination to be identical with the compound obtained in (b) above. A small amount (0·5 g.) of a liquid with a higher b. p. remained.

(d) *With an activated charcoal catalyst.* Activated charcoal (3 g.) was heated at 250° for 2 hr. *in vacuo* to remove adsorbed gases and was then sealed with chlorotrifluoroethylene (2·8 g., 0·024 mole) and hydrogen bromide (1·9 g., 0·024 mole). After 24 hours' heating at 90°, the products were distilled to give unchanged reactants (1·1 g.) and 1-bromo-2-chloro-1 : 1 : 2-trifluoroethane (3·6 g., 76%), b. p. 51·5—51·9°, n_D^{20} 1·3705, identical (infra-red spectrum) with the earlier specimens.

(e) *In silica with an excess of olefin.* The olefin (7·60 g., 0·065 mole) and hydrogen bromide (0·89 g., 0·011 mole) were exposed to ultra-violet light for 2 hr. A small amount of solid polymer was formed on the side of the tube nearer the lamp. Distillation gave unchanged chlorotrifluoroethylene, 1-bromo-2-chloro-1 : 1 : 2-trifluoroethane (1·85 g., 85% based on hydrogen bromide), and a residue (0·4 g.). The combined residues from several such experiments were distilled to give 1-*bromo*-2 : 4-*dichloro*-1 : 1 : 2 : 3 : 3 : 4-*hexafluorobutane* (4% based on hydrogen bromide), b. p. 130° (micro), n_D^{20} 1·386 (Found : C, 15·2; H, 0·5. $C_4HBrCl_2F_6$ requires C, 15·3; H, 0·3%), 1-*bromo*-2 : 4 : 6-*trichloro*-1 : 1 : 2 : 3 : 3 : 4 : 5 : 5 : 6-*nonafluorohexane* (0·5% based on hydrogen bromide), b. p. 140°/100 mm. (micro), n_D^{20} 1·405 (Found : C, 16·3; H, 0·8. $C_6HBrCl_3F_9$ requires C, 16·7; H, 0·2%), and a glass-like residue of average composition Br·$[CF_2·CFCl]_6$·H (Found : C, 18·5; H, 0·1. Calc. for $C_{12}HBrCl_6F_{18}$: C, 18·4; H, 0·1%).

Dehalogenation of 1-*Bromo*-2-*chloro*-1 : 1 : 2-*trifluoroethane*.—A solution of the compound (7·0 g.) in ethanol (15 ml.) was added to a well-stirred mixture of zinc dust (40 g.) and refluxing ethanol (100 ml.). After 8 hr. the gaseous product was washed with water and distilled *in vacuo* to give trifluoroethylene (2·5 g., 85%) (Found : *M*, 82. Calc. for C_2HF_3 : *M*, 82), identified by means of its infra-red spectrum. 1-Chloro-1 : 2-difluoroethylene was not produced.

Reaction of 1-*Bromo*-2 : 4-*dichloro*-1 : 1 : 2 : 3 : 3 : 4-*hexafluorobutane with Zinc and Dioxan*.—The compound (0·89 g.) was sealed in a Pyrex tube with zinc dust (2 g.) and dioxan (5 ml.) and heated to 100° for 24 hr. in a rocking furnace. The volatile products were washed with water, dried (P_2O_5), and distilled *in vacuo* to give 4-*chloro*-1 : 1 : 2 : 3 : 3 : 4-*hexafluorobut*-1-*ene* (0·42 g., 75%), b. p. 56° (isoteniscope) (Found : C, 24·3%; *M*, 197. C_4HClF_6 requires C, 24·2%; *M*, 198·5).

Infra-red Spectra.—These were recorded on a Perkin–Elmer Model 21 instrument with sodium chloride optics. Values are in μ (m = medium, s = strong, vs = very strong, w = weak).

$CHF_2·CF_2Br$ (vapour) : 3·36 (m), 4·40, 4·51 (m, doublet), 7·20 (s), 7·40 (s), 7·67 (w), 8·03 (vs), 8·34 (w), 8·57 (vs), 8·81 (vs), 9·33 (s), 10·32 (vs), 11·15 (m), 12·14 (vs), 13·45 (m), 15·05, 15·17 (m, doublet).

H·$[C_2F_4]_2$·Br (vapour) : 3·36 (w), 4·41 (w), 7·12 (m), 7·35 (m), 7·66 (s), 7·85 (s), 8·14 (s), 8·35 (vs), 8·73 (vs), 9·05 (s), 9·30 (m), 9·70 (w), 9·90 (w), 10·15 (m), 11·05 (m), 11·36 (m), 11·86 (s), 12·15 (s), 12·45 (s), 12·80 (s), 13·45 (vs), 14·33 (w).

CF_2·CF·CF_2·CHFCl (vapour) : 3·35 (w), 4·64 (w), 5·56 (s), 7·25 (m), 7·50 (m), 7·64 (m), 8·16 (m), 8·30 (m), 8·45 (vs), 8·60 (vs), 8·78 (s), 8·96 (s), 9·17 (s), 9·77 (s), 10·15 (m), 10·36 (m), 11·85 (s), 12·25 (s), 12·80 (s).

CF_2Br·CHFCl (vapour) : 3·35 (w), 4·56 (w), 7·47 (m), 7·87 (m), 8·15 (s), 8·67 (vs), 9·05 (vs), 9·52 (vs), 10·3 (vs), 11·0 (w), 11·7 (vs), 12·5 (s), 13·1 (m).

Br·$[CF_2·CFCl]_2$·H (liquid) : 3·34 (w), 7·43 (m), 7·48 (m), 8·01 (s), 8·42 (vs), 8·65 (vs), 8·99 (vs), 9·64 (s), 9·78 (s), 10·02 (w), 10·50 (s), 11·37 (m), 11·75 (m), 12·15 (m), 12·63 (w), 13·25 (w), 13·65 (m), 14·25 (w).

Br·$[CF_2·CFCl]_3$·H (liquid) : 3·3 (w), 7·42 (w), 7·90 (m), 8·45 (broad, vs), 8·7 (vs), 8·93 (vs), 9·07 (s), 9·77 (s), 10·34 (s), 11·25 (m), 11·77 (m), 12·50 (m), 13·65 (m), 14·45 (m).

Lacher, Lea, Walden, Olson, and Park (*J. Amer. Chem. Soc.*, 1950, **72**, 3231) assumed that in the charcoal-catalysed reaction of hydrogen bromide with chlorotrifluoroethylene the bromine became attached to the CF_2 group, and concluded that there was less than 0·2% of side reaction. Their infra-red spectrum of 1-bromo-2-chloro-1 : 1 : 2-trifluoroethane shows bands at 12·6 (s), 13·8 (m) and 14·4 (w) μ, however, which are not present in the spectrum of 1-bromo-2-chloro-1 : 1 : 2-trifluoroethane prepared photochemically.

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The Rates of Ionisation of 1 : 1-*Dimethylprop-2-ynyl Chloride and its 3-Alkyl Derivatives, and the Nature of the Baker–Nathan Effect.*

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The rates of solvolysis and of alkaline hydrolysis of 1 : 1-dimethylprop-2-ynyl chloride (3-chloro-3-methylbut-1-yne) and its 3-alkyl derivatives $CR{:}C{\cdot}CMe_2Cl$ in 80% ethanol and their hydrolysis in wet formic acid are determined. They proceed by the unimolecular mechanism, except for the bimolecular alkaline hydrolysis of 1 : 1-dimethylprop-2-ynyl chloride itself and possibly for its ethanolysis. The introduction of a 3-alkyl group produces 1000-fold acceleration of ionisation, establishing the ability of the C≡C bond to transmit polar effects strongly. The rates of the unimolecular reactions in 80% ethanol decrease in the order 3-Me > Et > Pr^i > Bu^t ≫ H, *i.e.*, the Baker–Nathan effect is observed. This effect is attributed to the steric inhibition of bond contraction and the resulting reduction of stabilisation of the R–C bonds increasing in the order Me ⟶ CMe_3 in the carbonium ions formed. Only inductive electron displacements are involved.

Normally the electron-donating power of alkyl groups increases in the order (H <) Me < Et < Pr^i < Bu^t. However, an (apparent) reversal of this order is often observed in chemical equilibria and reactions. This was first noted by Baker and Nathan (*J.*, 1935, **1844**) in the study of the kinetics of the bimolecular combination of 4-substituted benzyl bromides with pyridine.

This effect has always been observed in the unimolecular hydrolysis of substituted alkyl halides, in which ionisation is the rate-determining step. The results are summarised in Table 1. In the case of the bromides $R{\cdot}CH_2Br$ in moist formic acid there is some contribution from the bimolecular reaction, which is predominant with methyl bromide itself. The effect of alkyl groups in the corresponding tertiary chlorides appears to be irregular, but this has been attributed by Brown and Fletcher and by Brown and Stern (see footnotes to Table 1) to the contribution from an additional factor, namely, the relief by ionisation of the steric strain present in the original halide. In its absence, the Baker–Nathan effect would be more prominent, in particular, $Bu^t{\cdot}CMe_2Cl$ would ionise more slowly.

Table 1. *Rates of unimolecular hydrolyses of alkyl halides.**

Series	Solvent	Temp.	H	Me	Et	Pr^i	Bu^t
$R{\cdot}CH_2Br$ [1]	$H{\cdot}CO_2H$	95°	0·0174	0·027	0·0185	—	0·0153
$R{\cdot}CMe_2Cl$ [2]	80% EtOH	25	0·000019 †	0·092	0·153	0·081	0·111
$H_2C{:}CH{\cdot}CHRCl$ [3] ...	$H{\cdot}CO_2H$	44·6	0·000036 ‡	2·05	—	—	0·91
$RHC{:}CH{\cdot}CH_2Cl$ [3] ...	$H{\cdot}CO_2H$	44·6	0·000036 ‡	1·283	—	—	0·817
$p\text{-}RC_6H_4{\cdot}CH_2Br$ [4] ...	$H{\cdot}CO_2H$	25·1	0·00368	0·213	—	—	0·103
$p\text{-}RC_6H_4{\cdot}CHPhCl$ [5]...	80% $COMe_2$	25	0·728	15·6	12·6	10·04	7·96

* Values are given as 10^4k_1 (sec.$^{-1}$).
† Estimated by Cooper and Hughes from experiments at higher temperatures (*J.*, 1937, **1184**).
‡ Estimated by Vernon from experiments at higher temperatures (*loc. cit.*).

[1] Dostrovsky and Hughes, *J.*, 1946, 171. [2] Brown and Fletcher, *J. Amer. Chem. Soc.*, 1949, **71**, 1845; Brown and Stern, *ibid.*, 1950, **72**, 5068; Shorter and Hinshelwood, *J.*, 1949, 2412. [3] Vernon, *J.*, 1954, 423. This paper appeared after completion of the present investigation. [4] Bevan, Hughes, and Ingold, *Nature*, 1953, **171**, 301. [5] Hughes, Ingold, and Taher, *J.*, 1940, 949.

We considered it possible that a knowledge of the unimolecular solvolysis of compounds containing the various alkyl groups attached to triple bonds would throw light on the Baker–Nathan effect and the effect of alkyl groups in general, and have investigated conductimetrically the kinetics of the solvolysis of 1 : 1-dimethylprop-2-ynyl chloride and its 3-alkyl derivatives $CR{:}C{\cdot}CMe_2Cl$, where R = H, Me, Et, Pr^i, and Bu^t, in 80% aqueous ethanol, in the absence and in the presence of sodium hydroxide. Results are summarised in Table 2.

The solvolysis of 3-chloro-3-methylbut-1-yne is very slow at 25°. The initial rates

could be measured accurately and follow the kinetics of a first-order irreversible reaction (k_1, $8{\cdot}43 \times 10^{-4}$ hr.$^{-1}$). After 100 hr. (8% reaction) the velocity coefficient decreases, probably owing to irreversible side reactions in which hydrogen chloride is consumed. Favorskaya (*J. Gen. Chem., U.S.S.R.*, 1939, **9**, 386, 1237) and Hennion, Sheehan, and Maloney (*J. Amer. Chem. Soc.*, 1950, **72**, 3542) have shown that, in the presence of

TABLE 2. *Kinetic data for the solvolyses and alkaline hydrolyses of the compounds* $CR{:}C{\cdot}CMe_2Cl$ *in* 80% *ethanol.*

Reaction Temp.	10^4k_1, Alk. hydr. 25°	10^4k_1, Solv. 25°	10^4k_1, Solv. 25°	10^4k_1, Solv. 15°	$10^{12}B$, Solv.	E, Solv.
R = H	(7·1) *	0·00237	0·00234	—	—	—
Me	4·9	5·13	5·10	1·48	1·7	21·2
Et	4·6	4·90	4·90	1·415	1·7	21·2
Pr^i	3·45	3·42	3·41	0·934	5·8	22·1
Bu^t	2·77	2·80	2·78	0·768	4·1	22·0

k_1 and B are the first-order velocity constant and Arrhenius frequency factor in sec.$^{-1}$, respectively. E is the Arrhenius activation energy in kcal./mole. * Second-order velocity constant.

concentrated hydrochloric acid, isomerisation to 1-chloro-3-methylbuta-1 : 2-diene, $CHCl{:}C{:}CMe_2$, and 2-chloro-3-methylbuta-1 : 3-diene, $CH_2{:}CCl{\cdot}CMe{:}CH_2$, takes place. We have confirmed that isomerisation also occurs in our experiments. After the reaction mixture had been heated at 80° (in a stoppered flask) for 9 hr. to complete the reaction, the total content of ionised and labile chloride dropped to 81·5% of its original value, indicating approximately 18% isomerisation.

The alkaline hydrolysis of 3-chloro-3-methylbut-1-yne in 80% ethanol is much faster and follows the kinetics of a second-order irreversible reaction (k_2, $7{\cdot}1 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$). It occurs by a bimolecular mechanism. The products of this reaction were not examined, but the results of previous investigations of nucleophilic reactions of this and similar compounds have shown that normal nucleophilic substitution (S_N2), substitution with rearrangement (S_N2'), and elimination ($E2$) occur simultaneously, though in a varying degree (cf. Zakharova, *J. Gen. Chem., U.S.S.R.*, 1947, **17**, 688; Pudovik, *ibid.*, 1951, **21**, 1462, 1811).

Our determinations do not allow a decision whether the solvolysis (in absence of alkali) occurs by the unimolecular or by the bimolecular mechanism, or whether both mechanisms occur simultaneously. Pudovik (*loc. cit.*) measured the rates of solvolysis of this substance in 50% ethanol and in 40% acetone at 35° (k_1, 0·132 and 0·08 hr.$^{-1}$, respectively) and, in spite of the absence of conclusive evidence, suggested that the solvolysis is unimolecular.

A comparison with data available for other compounds suggests that the bimolecular reaction could make an appreciable contribution. Thus, the ratio k_2/k_1, where k_2 and k_1 are the velocity constants for the alkaline hydrolysis and solvolysis in 80% ethanol respectively, is 3000 : 1 in the case of 3-chloro-3-methylbut-1-yne. For methyl and ethyl bromide, which are known to undergo solvolysis by the bimolecular mechanism, the corresponding ratios are of the same order (6000 : 1 and 1250 : 1, respectively).

The rates of solvolysis in 80% ethanol of the 3-alkyl-1 : 1-dimethylprop-2-ynyl chlorides ($RC{:}C{\cdot}CMe_2Cl$; where R is Me, Et, Pr^i, and Bu^t) measured at 25° (in duplicate) and at 15° are much faster and not affected by the presence of alkali. The rate-determining step in these reactions is thus the ionisation of the alkyl chloride.

The solvolyses follow the kinetics of first-order irreversible reactions up to about 60—75% of reaction. Beyond that point allowance must be made for the reversibility of solvolysis and, possibly, of the ionisation itself. The equilibrium positions corresponded to approximately 92—98% of reaction, but except with the *tert.*-butyl derivative they could not always be determined exactly because the reversible hydrolyses are accompanied by slower irreversible reactions (such as hydrogen chloride elimination). Hence, the velocity coefficients for the final stages of the reactions are in some cases slightly unreliable. However, we have established that no hydrogen chloride is consumed in irreversible

reactions such as the formation of isomeric chlorides or addition to the triple bond. The velocity coefficients for the solvolyses in presence of sodium hydroxide at 25°, calculated for first-order irreversible reaction, are reasonably constant and almost identical with those found in absence of alkali.

The rates of unimolecular solvolysis of the compounds CR:C·CMe_2Cl increase in the order $H \ll Bu^t < Pr^i < Et < Me$. Table 2 also shows the Arrhenius activation energies and frequency factors for solvolysis (except for the parent substance, the mechanism of solvolysis of which is uncertain). The activation energies tend to increase from the methyl to the *tert.*-butyl derivative, but too much significance cannot be attached to the numerical values obtained since the Arrhenius activation energy is known to be not quite representative of the true activation energy (corresponding to the potential-energy difference). The inadequacy of the Arrhenius equation probably explains also the variation in the frequency factor B, which is roughly parallel to the smaller variation in E (cf. Hammett, "Physical Organic Chemistry," McGraw-Hill, New York, 1940, 184 *et seq.*; Moelwyn-Hughes, "The Kinetics of Reactions in Solution," Oxford Univ. Press, 1947, 266 *et seq.*).

The hydrolysis in formic acid containing small amounts of water has also been investigated, the rates being followed by the titration methods developed by Bateman and Hughes (*J.*, 1937, 1187; 1940, 940, 945). The velocity coefficients for 3-chloro-3-methylbut-1-yne at 25°, calculated for a first-order reversible reaction, were found to be independent of the concentration of water (0·4 and 0·5% respectively), showing that ionisation of the molecule is the rate-determining step. However, the reaction is not free from complications causing a decrease of the calculated velocity coefficients with time. This is due to consumption of hydrogen chloride in irreversible reactions, as shown by a decrease in time of the total labile and ionised chloride content (cf. comments on the solvolysis in 80% ethanol) and possibly to irreversible elimination which is followed by addition of water to the elimination product (cf. Rupe and Kambli, *Helv. Chim. Acta*, 1926, **9**, 672; Hennion, Davis, and Maloney, *J. Amer. Chem. Soc.*, 1949, **71**, 2813).

These kinetic complications were eliminated by the addition of an excess of calcium formate to the reaction mixture to remove the free hydrogen chloride as liberated. The reaction is still unimolecular, in spite of the possibility of some nucleophilic action by the formate ion (cf. Bateman and Hughes, *loc. cit.*), since the velocity coefficients calculated for a first-order reversible reaction are constant (at 15°; k_1, $2{\cdot}7 \times 10^{-2}$ hr.$^{-1}$).

The 3-alkyl homologues were also hydrolysed under the same conditions, but the rapidity of their hydrolysis and the very considerable experimental error involved did not allow the determination of velocity constants of sufficient accuracy to measure their small differences. Their hydrolysis is approximately 5000 times faster than that of the parent hydrogen compound.

Originally, a few experiments were carried out with prop-2-ynyl bromide in wet formic acid at 75°, but no free hydrogen bromide had been liberated after 3 hr. Addition of hydrogen bromide to the triple bond is quite rapid at this temperature but hydrolysis is very slow. This is similar to the findings of Hatch and Chiola (*J. Amer. Chem. Soc.*, 1951, **73**, 361), who attempted to measure the rates of hydrolysis of prop-2-ynyl chloride and its 3-methyl homologue in aqueous hydrochloric acid, in the presence and in the absence of cuprous chloride, and observed the addition of hydrogen chloride to the triple bond. The investigation of this series of halides appeared unpromising and was discontinued in favour of that of the tertiary halides discussed.

Discussion

The effect of solvation being ignored, the rate of ionisation of an alkylhalide will depend on two factors: (1) The energy of heterolytic fission of the C–Hal bond resulting in the formation of a cation (or a transition state) possessing linkages identical with those in the original undissociated molecule: this will decrease with the increasing electron-donating character of the substituents in the original molecule. (2) The energy of stabilisation of (all the individual linkages in) the cation (or transition state) formed: this is generally

assumed to increase with the electron-donating inductomeric or electromeric electron displacements.

The Nature of the Baker–Nathan Effect.—This effect as observed in the unimolecular hydrolysis (ionisation) of the 3-alkyl-1 : 1-dimethylprop-2-ynyl chlorides (Table 2) and of other series of alkyl halides (Table 1) is generally attributed to hyperconjugation; *i.e.*, idealised structures involving H^+, such as H^+ $H_2C{:}C{:}C{:}CH_2$ in the case of 3-alkyl-1 : 1-dimethylprop-2-ynyl chlorides, are assumed to contribute strongly to the stability of the cations. It is, therefore, noteworthy that in the series $R{\cdot}CMe_2X$, $R{\cdot}CH{:}CH_2X$, $H_2C{:}CH{\cdot}CHRX$, and $RC{:}C{\cdot}CMe_2X$ the rates of ionisation of the *tert.*-butyl derivatives ($R = Bu^t$) are a few thousand times greater than those of the corresponding parent substances ($R = H$), although hyperconjugation involving structures containing H^+ is not possible, and that, in contrast, the increase on replacement of a methyl group in *tert.*-butyl by a hydrogen atom is only very small (about 25%).

This very considerable effect of the *tert.*-butyl group can be attributed to an inductive effect within the undissociated alkyl halide causing a reduction of the energy of heterolytic fission of the C–Hal bond (1) and to an increased stabilisation of the cation involving an inductive electron displacement (2). In this case, each of the three substituting methyl groups in *tert.*-butyl can only be responsible for less than one-sixth of the total inductive effect of this group. Thus, hyperconjugation involving one C–H bond, if it exists, could also contribute only a similar amount to the total electronic effect, although it could be expected to be more pronounced in the carbonium ions than in any other known system. It would be of the same order of magnitude as the inductive effect of the substituting methyl groups, irrespective of whether the alkyl groups are attached to a double bond, a triple bond, or directly to the C atom acquiring a positive charge. This interpretation requires the replacement of one appreciable electronic effect by an alternative one of the same magnitude, in order to account for some small differences.

This view also implies that the hyperconjugative electron displacement increases more strongly than the inductive one as the electron-demand increases. Thus, in simple neutral molecules such as propene and propyne, in which hyperconjugation has been claimed to be the main factor responsible for the shortened C–C bond distances and increased C–C bond energies (Pauling, Springall, and Brown, *J. Amer. Chem. Soc.*, 1939, **61**, 927; Mulliken, *J. Chem Phys.*, 1939, **7**, 339; Mulliken, Rieke, and Brown, *J. Amer. Chem. Soc.*, 1941, **63**, 41), it could only make a much smaller contribution than in the carbonium ions. The observed effects scarcely necessitate this hypothesis. This is supported by a consideration of the energetics of hyperconjugation. The energy differences between structures such as H^+ $H_2C{:}CH{\cdot}\bar{C}H_2$ and H^+ $H_2C{:}C{:}\bar{C}H$ and the corresponding conventional structures $H_3C{\cdot}CH{:}CH_2$ and $H_3C{\cdot}C{:}CH$ respectively are not less than 370 kcal., since they involve at least the ionisation of a hydrogen atom (312 kcal.) and the homolytic fission of a C–H bond (100 kcal.). Even in the 3-methylprop-2-ynyl cation the difference in energy between $H_3C{\cdot}C{:}C{\cdot}\overset{+}{C}H_2$ and H^+ $H_2C{:}C{:}C{:}CH_2$ is at least 130 kcal.

Alternatively, the considerable effect of the *tert.*-butyl group could be attributed to a contribution from hyperconjugated structures involving $\overset{+}{C}H_3$ instead of H^+ such as $H_3\overset{+}{C}$ $CMe_2{:}C{:}C{:}CMe_2$ (cf. Berliner and Bondhus, *J. Amer Chem. Soc.*, 1948, **70**, 854; Vernon, *loc. cit.*). This view would be able to account for the Baker–Nathan effect if one assumes that hyperconjugation involving H^+ structures would make only a slightly greater contribution than that involving $\overset{+}{C}H_3$ structures (and some smaller contribution from the inductive effect), that both types of hyperconjugation would make similar, but now possibly the main contributions to the stability of the cations, and that somehow the H^+ hyperconjugation would increase more strongly than $\overset{+}{C}H_3$ hyperconjugation with increasing electron demand. It should, therefore, be noted that the energy required to form a proton is about 100 kcal. greater than that required to form a methyl cation, since the bond energy of the C–C linkage (80 kcal.) is about 20 kcal. less than that of C–H, and the ionisation potential of the hydrogen atom (312 kcal.) exceeds that of the methyl radical (231 kcal.;

cf. Price, *loc. cit.*) by about 80 kcal. Thus, Me^+ hyperconjugation, if existing, should be more important than that involving H^+, which would be at variance with the factual requirements.

What is possibly even more important, the hypothesis of hyperconjugation cannot explain why the Baker–Nathan effect is observed in the basicities of the aliphatic amines $R{\cdot}NH_2$ (Table 3), for which hyperconjugated structures cannot be formulated, and why it is not observed in the ionisation potentials of the alkylbenzenes (Table 3), although they involve the formation of molecule ions.

TABLE 3.

Property	Compound	R = H	Me	Et	Pr^i	Bu^t
pK	$R{\cdot}NH_2$ [1]	9·27	10·64	10·67	10·63	10·45
I.P. (eV)	$R{\cdot}C_6H_5$ [2]	9·24	8·92	8·75	8·6	8·5

[1] Hall and Sprinkle, *J. Amer. Chem. Soc.*, 1930, **52**, 5115; 1932, **54**, 3469. [2] Price, *Chem. Reviews*, 1947, **41**, 257.

It has already been shown (Burawoy, *Trans. Faraday Soc.*, 1944, **40**, 537; *Chem. and Ind.*, 1944, **51**, 434; "Contribution à l'Étude de la Structure Moléculaire," Desoer, Liége, 1947/48, p. 73) that the valency conception of non-localised bonds, which forms also the basis of the hypothesis of hyperconjugation, is in disagreement with numerous observations and is not required to explain the constitutive changes of covalent linkages. They can be accounted for less ambiguously and more consistently by a consideration of inductive electron displacements only which originate in changes of the effective nuclear charges at individual atoms (their screening). An increase of the positive charge at the C atom of a linkage C–X will be responsible for a "stereomeric" effect, *i.e.*, an attraction of the electrons shared with X accompanied by a shortening and strengthening of the bond. The magnitude of the changes will depend on the polarisability of the electronic system of X and on the increasing repulsive interaction between the nuclei and between the inner orbit electrons respectively of C and X resisting bond contraction and stabilisation. The steric repulsions between the groupings attached to C and those attached to X will also play a part (for a more detailed discussion illustrated by examples, see Burawoy, *loc. cit.*).

This view leads to an interpretation of the Baker–Nathan effect which is similar to one already suggested for the apparent inversion of the normal polar effect of the halogen atoms sometimes observed in chemical changes (Burawoy, 1947/48, *loc. cit.*). Thus, the polarity of the C–Hal bond in the original alkyl halide molecule $R{\cdot}CH_2{\cdot}Hal$ will increase and its energy of heterolytic fission will be reduced in the order of the increasing electron-donating inductive effect of the alkyl groups R (factor 1). On the other hand, in the cations $R{-}\overset{+}{C}H_2$ formed (or the transition state obtained during ionisation) the contraction and stabilisation of the $R{-}C^+$ bond will be reduced by the steric repulsions increasing with the size of the alkyl groups R (factor 2). The magnitude of the stabilisation energy (and its reduction due to the steric inhibition of bond contraction) will increase as the effective nuclear charge at the C^+ atom increases. Factor 1 will facilitate ionisation in the order $Me < Et < Pr^i < Bu^t$, factor 2 in the reverse order. In the ionisation of the alkyl halides, the latter factor is more important and, therefore, a Baker–Nathan effect is observed.

This interpretation is free from the inconsistencies resulting from the introduction of hyperconjugation. It is strongly supported by the fact that the Baker–Nathan effect is encountered only in chemical equilibria and other changes in which bond stabilisations and bond contractions within one of the two entities involved play an important part, and that it is not observed in physical properties such as dipole moments, ionisation potentials (cf. below), and, as will be shown elsewhere, electronic spectra, which do not involve bond contractions.

It explains the Baker–Nathan effect observed in the basicities of the aliphatic amines $R{\cdot}NH_2$. In this case the effect is less pronounced, because the increase of the effective nuclear charge at the N atom in the ammonium ions $R{\cdot}\overset{+}{N}H_3$, which determines the

stabilisation energy, will be due to the addition of a proton and will be smaller than that at the charged C atom in the carbonium ions due to a removal of an electron pair.

The decrease of the ionisation potentials of alkylbenzenes in the order of substituents Me > Et > Pr^i > Bu^t is also accounted for. The ionisation potentials derived from spectroscopic data depend on the inductive electron-donating effect of the alkyl groups, *i.e.*, the polarisability of the electronic system. They do not involve changes of interatomic distances in the molecule ion formed and, thus, are not affected by any steric inhibition of bond contraction which is responsible for the Baker–Nathan effect.

The Effect of 3-*Alkyl Groups.*—The acceleration of ionisation of the investigated 3-alkyl-1 : 1-dimethylprop-2-ynyl chlorides as well as of the 3-alkylallyl chlorides discussed by Vernon (*loc. cit.*) on replacement of a $C_{(3)}$-hydrogen atom by an alkyl group is of the same magnitude as that caused by the introduction of an alkyl group in the 1-position (cf. Table 1). This shows that a triple bond (like a double bond) strongly transmits the stereomeric effect, *i.e.*, the increased effective nuclear charge, from the 1- to the 3-position. One might have expected that the effect of the alkyl groups would decrease with their distance from the C–Hal bond and the charged atom in the cation respectively, but this may be balanced by the greater electron-donating character of alkyl groups when attached to multiple linkages. The smaller rate increase due to alkyl groups substituted in the *para*-position of a phenyl group may be due to the former factor.

The Effect of the Ethynyl Group.—Bartlett and Rosen (*J. Amer. Chem. Soc.*, 1942, **64**, 543) and Hatch and Chiola (*loc. cit.*) found that primary prop-2-ynyl halides react with potassium iodide 50—100 times as fast as do the corresponding saturated halides; *i.e.*, the replacement of hydrogen by an ethynyl group produces an acceleration of nucleophilic substitution by the bimolecular mechanism. Comparing the ethynyl with the ethyl group, Zakharova and Dobromyslova (*J. Gen. Chem., U.S.S.R.*, 1950, **20**, 2029) pointed out that the electron-attracting effect of the ethynyl group should facilitate attack by a nucleophilic reagent, but hinder ionisation. This is true, but our experiments show that the ionisation of 1 : 1-dimethylprop-2-ynyl chloride in 80% ethanol at 25° is approximately 100 times faster than that of *iso*propyl chloride (cf. Table 1), *i.e.*, the replacement of *hydrogen* by an ethynyl group facilitates ionisation. This establishes that the expected appreciable increase of the energy of heterolytic fission of the C–Cl bond due to the electron withdrawal by the ethynyl group is counterbalanced by an even greater increase in the energy of stabilisation of the carbonium ion (or transition state) resulting mainly from the polarisation and contraction of the $C_{C\equiv C}$–C^+ bond.

Experimental

Preparations.—1 : 1-Dimethylprop-2-ynyl chloride and its homologues were prepared by the general route: acetylene → acetylenic alcohol → acetylenic chloride. All acetylenic alcohols and chlorides were purified by alternate fractional distillation under reduced pressure and fractional crystallisation. Most of the m. p.s have not been recorded previously.

2-*Methylbut*-3-*yn*-2-*ol.*—This alcohol was prepared by the action of acetone on sodium acetylide in liquid ammonia (Campbell, Campbell, and Eby, *J. Amer. Chem. Soc.*, 1938, **60**, 2882); it had b. p. 104°/760 mm., m. p. 2° (Campbell and Eby, *ibid.*, 1941, **63**, 2683, give 2°).

3-*Chloro*-3-*methylbut*-1-*yne.*—The chloride was prepared by treatment of 2-methylbut-3-yn-2-ol with concentrated hydrochloric acid (Hennion, Sheehan, and Maloney, *loc. cit.*); it had b. p. 75°/760 mm., m. p. —61° (Found: Cl, 34·3. Calc. for C_5H_7Cl: Cl, 34·6%).

2-*Methylpent*-3-*yn*-2-*ol.*—This alcohol is not obtainable in appreciable yields by the action of acetone on sodium methylacetylide in either liquid ammonia or ether. It was prepared by the action of acetone on prop-1-ynylmagnesium bromide (Hurd and Cohen, *ibid.*, 1931, **53**, 1068; Zakharova, *J. Gen. Chem., U.S.S.R.*, 1947, **17**, 688); the acetylenic Grignard compound was obtained by passing methylacetylene (15% excess) into ethereal ethylmagnesium bromide at −25°; it had b. p. 80°/100 mm., 134°/760 mm., m. p. −13·5°, d_4^{20} 0·8763 (Found: C, 73·3; H, 10·0. Calc. for $C_6H_{10}O$: C, 73·4; H, 10·3%).

4-*Chloro*-4-*methylpent*-2-*yne.*—Into a mixture of pure 2-methylpent-3-yn-2-ol (68·5 g.), light petroleum (b. p. <40°, 200 c.c.), finely powdered calcium chloride (20 g.), and quinol (1 g.)

dry hydrogen chloride was passed for 4 hr. with vigorous stirring, at 0°. The light petroleum layer was decanted, shaken with anhydrous potassium carbonate, and dried ($MgSO_4$). After removal of the solvent and fractionation of the residue, 4-chloro-4-methylpent-2-yne (51 g., 62·5%) had b. p. 63°/100 mm., m. p. −5·1°, d_4^{25} 0·9247 (Found: C, 62·2; H, 7·4; Cl, 29·6. Calc. for C_6H_9Cl: C, 61·8; H, 7·8; Cl, 30·4%). Hurd and Cohen (*loc. cit.*) and Zakharova (*loc. cit.*) claimed to have prepared 2-methylpent-3-yn-2-ol and 4-chloro-4-methylpent-2-yne, but the former authors obtained an alcohol boiling at 75—77°/15 mm. and yielding a chloride of b. p. 57—61°/47 mm., and the latter an alcohol and chloride boiling at 80°/100 mm. and 60°/100 mm., respectively. Our products are identical with those obtained by Zakharova. Moreover, in physical properties they resemble the other members of the series so strongly as to leave no doubt as to their identities.

2-Methylhex-3-yn-2-ol.—This alcohol was obtained by the action of acetone on but-1-ynylmagnesium bromide (cf. Dupont, *Compt. rend.*, 1909, **148**, 1524; Picon, *ibid.*, 1914, **158**, 1184); b. p. 75°/60 mm., 144°/760 mm., m. p. −6° (Found: C, 74·4; H, 10·5. Calc. for $C_7H_{12}O$: C, 74·9; H, 10·8%).

2-Chloro-2-methylhex-3-yne.—Pure 2-methylhex-3-yn-2-ol (80 g.), dissolved in light petroleum (b. p. <40°; 200 c.c.), was treated with dry hydrogen chloride in presence of powdered calcium chloride (24 g.) and quinol (1 g.). *2-Chloro-2-methylhex-3-yne* was worked up like 4-chloro-4-methylpent-2-yne; it (62·4 g., 67%) had b. p. 76°/100 mm., m. p. −62°, d_4^{25} 0·9035 (Found: C, 64·1; H, 8·7; Cl, 27·0. $C_7H_{11}Cl$ requires C, 64·4; H, 8·5; Cl, 27·1%).

2 : 5-Dimethylhex-3-yn-2-ol.—To a solution of ethylmagnesium bromide [obtained from magnesium (54 g.), ethyl bromide (132 g.), and dry ether (720 c.c.)] 3-methylbut-1-yne (84 g.) dissolved in dry ether (125 c.c.) was added dropwise (1 hr.) with mechanical stirring and ice-cooling. After 24 hr. pure acetone (70 g.) was added dropwise, and the mixture set aside for 24 hr., refluxed finally for 30 min., and poured on ice (2000 g.) and 1 : 1 hydrochloric acid (400 c.c.). The product was extracted with ether. After being dried (K_2CO_3) and subsequent removal of the ether, *2 : 5-dimethylhex-3-yn-2-ol* was fractionated; the alcohol (98·5 g., 65%) had b. p. 148°/760 mm., m. p. −6·5°, d_4^{20} 0·8438 (Found: C, 75·8; H, 11·1. $C_8H_{14}O$ requires C, 76·1; H, 11·2%).

2-Chloro-2 : 5-dimethylhex-3-yne.—This compound was obtained by the action of dry hydrogen chloride on 2 : 5-dimethylhex-3-yn-2-ol (50 g.) in light petroleum (60 c.c.) in the presence of calcium chloride (15 g.) and quinol (0·5 g.), by the procedure used for 4-chloro-4-methylpent-2-yne; the *chloride* (34·5 g., 60%) had b. p. 79°/100 mm., m. p. −48°, d_4^{25} 0·8790 (Found: C, 66·0; H, 8·8; Cl, 24·2. $C_8H_{13}Cl$ requires C, 66·4; H, 9·1; Cl, 24·5%).

2 : 5 : 5-Trimethylhex-3-yn-2-ol.—This alcohol, prepared according to Hennion and Bannigan (*J. Amer. Chem. Soc.*, 1946, **68**, 1202), had b. p. 150°/760 mm., m. p. 32° (Hennion and Bannigan give 32°).

5-Chloro-2 : 2 : 5-trimethylhex-3-yne.—This chloride, prepared according to Hennion and Bannigan (*loc. cit.*), had b. p. 81°/100 mm., m. p. 17° (Hennion and Bannigan give 15°) (Found: Cl, 22·1. Calc. for $C_9H_{15}Cl$: Cl, 22·3%).

Rate Determinations.—Solvolyses in 80% aqueous ethanol. About 1 ml. of freshly purified halide was added to about 100 ml. of solvent (both at the required temperature), giving solutions M/12—M/20 with respect to alkyl halide. The same solvent (ethanol : water = 4 : 1 by vol.) was used for all solvolyses. The solvent used for the alkaline hydrolyses (ethanol : water : N-NaOH = 8 : 1 : 1) was made up freshly before each determination. The thermostatic control was accurate to ±0·01°.

The amount of hydrogen chloride liberated after various reaction times was determined conductimetrically. The conductivity bridge employed had a discrimination of at least 1 part in 1000. For each set of experimental conditions a calibration chart was prepared showing conductivity against amount of hydrogen chloride added, the relation being not quite linear. The resistance of the platinum electrode cell was checked before each rate determination. An allowance was made for the change in the conductivity of the solvent (by about 1%) due to the addition of about 1% (by volume) of alkyl halide.

In solvolysis the amount of hydrogen chloride liberated was measured directly, no other electrolyte being present, and a high degree of accuracy and reproducibility could be attained. The data for the alkaline solvolysis (hydrolysis) are less accurate since the conversion of sodium hydroxide into sodium chloride is accompanied by a much smaller change in conductivity. Moreover, the electrode was slightly less reliable in alkaline solution. In solvolysis the total amount of chloride present (ionised and labile organic) was estimated by titration of a sample of the reaction mixture by Volhard's method. In alkaline hydrolyses, which are irreversible,

the amount of chloride present initially was taken to be identical with the total hydrogen chloride liberated after completion of the reaction.

The results are illustrated by a few characteristic examples. Except for the alkaline hydrolysis of 4-chloro-4-methylpent-2-yne, only half the data available are reproduced, but the mean velocity coefficient is calculated from all measurements, some of the less reliable initial values (given in parentheses) being ignored.

Alkaline hydrolysis of $CH{\vdots}C{\cdot}CMe_2Cl$ *at* 25°.

Init. [RCl] = 4·84 ml. of 1N.

t (hr.)	0·5	0·75	1·0	2·0	3·0	3·5	4·0	5·0	6·0	16·1	∞
HCl (ml. of 1N)	0·53	0·80	1·03	1·8	2·35	2·6	2·8	3·2	3·45	4·52	4·84
k_2 (l. mole^{-1} hr.$^{-1}$)	(2·33)	2·49	2·48	2·54	2·52	2·55	2·55	2·65	2·63	2·50	—

k_2 (mean) = 2·56 l. mole^{-1} hr.$^{-1}$.

Solvolysis of $CH{\vdots}C{\cdot}CMe_2Cl$ *at* 25°.

Init. [RCl] = 8·88 ml. of 1N.

t (hr.)	7	10	23	25	30	35	47·1	50	102·2	150
HCl (ml. of 1N)	0·053	0·075	0·172	0·186	0·224	0·259	0·344	0·365	0·73	1·044
10^4k_1 (hr.$^{-1}$)	8·51	8·38	8·51	8·48	8·51	8·45	8·39	8·39	8·39	(8·33)

k_1 (mean) = 8·43 × 10^{-4} hr.$^{-1}$ (duplicate determination, 8·53 × 10^{-4}).

$CMe{\vdots}C{\cdot}CMe_2Cl$ at 25°

Alkaline hydrolysis

Init. [RCl] = 3·9 ml. of 1N

t (sec.)	HCl (ml. 1N)	10^4k_1 (sec.$^{-1}$)
450	0·7	4·40
600	0·95	4·65
750	1·17	4·75
900	1·4	4·95
1200	1·7	4·77
1500	2·05	4·97
1800	2·3	4·95
2700	2·9	5·05
3600	3·3	5·20
7200	3·8	5·08
∞	3·9	—

k_1 (mean) = 4·9 × 10^{-4} sec.$^{-1}$.

Solvolysis

Init. [RCl] = 7·3 ml. of 1N

t (sec.)	HCl (ml. 1N)	10^4k_1 (sec.$^{-1}$)
223	0·77	(5·01)
317	1·08	5·05
396	1·35	5·16
524	1·73	5·16
766	2·35	5·07
936	2·75	5·05
1198	3·35	5·13
1500	3·87	5·04
1800	4·39	5·11
2100	4·60	5·12
2400	5·15	5·09
3000	5·69	5·13
3600	6·07	5·09
14,400	7·13 *	—

k_1 (mean) = 5·1 × 10^{-4} sec.$^{-1}$.

$Me_3C{\cdot}C{\vdots}CMe_2Cl$ at 25°

Alkaline hydrolysis

Init. [RCl] = 5·5 ml. of 1N

t (sec.)	HCl (ml. 1N)	10^4k_1 (sec.$^{-1}$)
600	1·0	3·35
750	1·15	3·13
900	1·3	3·00
1200	1·6	2·87
1500	1·9	2·83
1800	2·15	2·75
2700	2·82	2·67
3600	3·4	2·67
4200	3·7	2·63
4800	3·93	2·61
6000	4·40	2·61
7200	4·65	2·68
10,800	5·1	2·60
∞	5·5	—

k_1 (mean) = 2·77 × 10^{-4} sec.$^{-1}$.

Solvolysis

Init. [RCl] = 5·13 ml. of 1N

t (sec.)	HCl (ml. 1N)	10^4k_1 (sec.$^{-1}$)
291	0·39	(2·71)
403	0·53	2·73
638	0·83	2·78
982	1·24	2·82
1295	1·57	2·82
1752	1·98	2·78
2100	2·25	2·75
2700	2·71	2·78
3000	2·88	2·75
3600	3·25	2·74
4800	3·75	2·78
6000	4·11	2·77
10,800	4·77	2·78
28,800	4·98 *	—

k_1 (mean) = 2·78 × 10^{-4} sec.$^{-1}$.

* Equilibrium.

Hydrolyses in Wet Formic Acid.—The experimental technique used to measure the comparatively slow hydrolysis of 1 : 1-dimethylprop-2-ynyl chloride was that employed by Bateman and Hughes for *tert.*-butyl chloride (*loc. cit.*). Samples were poured into carbon tetrachloride, which was extracted with water, and the halide content was estimated with silver nitrate.

Hydrolysis of $CH{\vdots}C{\cdot}CMe_2Cl$ *in formic acid at* 15°.

Init. [RCl] = 37·8 ml. of 0·01N; $[H_2O]$ = 1%; $[Ca(H{\cdot}CO_2)_2]$ = 0·6%.

t (hr.)	2	4·05	6	8	10	12	25	75	101
HCl (ml. of 0·01N)	2·3	3·9	5·4	7·2	8·4	10·3	18·5	33·3	35·6
10^2k_1 (hr.$^{-1}$)	(3·1)	2·7	2·5	2·6	2·5	2·7	2·7	2·8	2·8

k_1 (mean) = 2·7 × 10^{-2} hr.$^{-1}$ = 7·5 × 10^{-6} sec.$^{-1}$.

The alkyl derivatives of 1 : 1-dimethylprop-2-ynyl chloride are hydrolysed very rapidly under the same conditions, and some modification of the experimental method was necessary. The reaction was stopped by addition of a mixture of carbon tetrachloride and chloroform at −60°, the formic acid solidifying. Ice-water was added, and the mixture shaken. When all the material had liquefied the organic layer was separated without delay, and the hydrogen chloride in the aqueous layer was estimated as before. The results clearly show that further

hydrolysis occurred during the extraction of the hydrochloric acid with water, causing the apparent velocity coefficient to be too high, especially after the shorter reaction times.

Hydrolysis of $Me{\cdot}C{\equiv}C{\cdot}CMe_2Cl$ *in formic acid at* 15°.

Init. [RCl] = 36 ml. of 0·01N; $[H_2O]$ = 1%; $[Ca(H{\cdot}CO_2)_2]$ = 0·6%.

t (sec.)	5	15	15	30	30	45	60
HCl (ml. of 0·01N)	12·7	22·7	22	29·9	28	31·5	33·6
10^2k_1 (sec.$^{-1}$)	8·7	6·6	6·3	5·9	5·0	4·6	4·4

k_1 (extrapolated) = $\sim 4 \times 10^{-2}$ sec.$^{-1}$.

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The Thorium–Tellurium System.

By R. W. M. D'EYE and P. G. SELLMAN.

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From *X*-ray and chemical analysis, phase-rule considerations, and tensimetric studies the compounds ThTe, $ThTe_2$, $ThTe_{2\cdot66}$, and ThOTe have been identified. ThTe possesses primitive cubic symmetry, with one molecule per unit cell, and is not isostructural with ThS or ThSe. ThTe, in contrast to the corresponding sulphide and selenide which melt above 1800° c, is degraded well below 1000° c *in vacuo*. Owing to the apparent low symmetry of $ThTe_2$ and $ThTe_{2\cdot66}$ complete crystal-structure data have so far not been obtained. No telluride corresponding to Th_2X_3, Th_7X_{12}, or $ThX_{2\cdot33}$ (where X = S or Se) has been found, and it would appear that the Th–Te system is not analogous to the Th–S or the Th–Se system. The ternary compound ThOTe is isostructural with ThOS and ThOSe; it is tetragonal with 2 molecules per unit cell. ThOTe is degraded when heated *in vacuo* into its constituents, whereas ThOSe melts without degradation at 2200° c.

THE thorium–selenium system (D'Eye, Sellman, and Murray, *J.*, 1952, 2555; D'Eye, *J.*, 1953, 1670) is analogous to the thorium–sulphur system (Eastman, Brewer, Bromley, Gilles, and Lofgren, *J. Amer. Chem. Soc.*, 1950, **72**, 40; Zachariasen, *Acta Cryst.*, 1949, **2**, 291; A.E.C.D. 2141). In view of the general lack of information regarding the tellurides of the heavy elements we investigated the thorium–tellurium system to see if it is analogous to the systems just mentioned.

Montignie (*Bull. Soc. chim.*, 1947, **14**, 748) claimed to have prepared Th_3Te by reduction of $ThTeO_4,8H_2O$ with hydrogen at 400°. However in our work we found no telluride lower than ThTe. A uranium telluride UTe_2 (impure product only) was also claimed by Montignie (*loc. cit.*), but Colani (*Compt. rend.*, 1903, **137**, 383; *Ann. Chim. Phys.*, 1907, **12**, 87) had previously reported only UTe and U_2Te_3, prepared respectively by reducing $NaCl,UCl_4$ with hydrogen at 1000° and by double decomposition of $2NaCl,UCl_4$ with Na_2Te. He was unable to find a compound of composition UTe_2.

From a consideration of the increase in size of the anion it seemed unlikely that the Th–Te system would be completely analogous to the Th–S and the Th–Se system. This has been found to be the case. Three tellurides have been identified, ThTe, $ThTe_2$, and $ThTe_{2\cdot66}$ (Th_3Te_8), and an oxytelluride ThOTe. This is in contrast to the five selenides ThSe, Th_2Se_3, Th_7Se_{12}, $ThSe_2$, and $ThSe_{2\cdot33}$ (Th_3Se_7) and the oxyselenide ThOSe. Only the oxytelluride and oxyselenide were found to be isostructural.

EXPERIMENTAL

Samples with compositions ranging from $ThTe_{0\cdot1}$ to $ThTe_5$ were prepared from their components *in vacuo* in the temperature range 600—1100°. However, as degradation of the resulting products *in vacuo* had started at temperatures of 500°, it was not possible to render the products homogeneous by melting, which further meant that metallographic studies and thermal analysis became impracticable.

(a) *Preparation.*—(i) *Thorium tellurides.* Intimate mixtures of thorium and tellurium in the requisite proportions were placed in fused quartz tubes which were then evacuated to

10^{-5} mm. and sealed. The thorium had been previously thoroughly outgassed by heating it *in vacuo*. The bombs were slowly heated to 400° in a tube furnace, thereby allowing a fair quantity of the tellurium to be absorbed by the thorium before a strongly exothermic reaction started at 400°. The temperature could then be safely raised to the annealing temperature. When the sealed tubes were to be heated at or above 1000° they were placed in a tube which could be evacuated to 10^{-5} mm. This prevented any diffusion of gas through the walls of the silica bomb which would cause oxidation of the specimen to ThOTe and/or ThO_2.

To prevent the initial violent reaction between thorium and tellurium the apparatus shown in Fig. 1 was used. The requisite amounts of the elements were placed in separate limbs of the H-shaped apparatus. The limb containing the thorium was closed by a thin glass septum which could be broken when necessary by a pointed breaker. The apparatus was evacuated to 10^{-5} mm. and sealed off at the constriction *B*. It was then placed in an oven at a temperature sufficient to give a vapour pressure of tellurium of a few mm. (Brooks, *J. Amer. Chem. Soc.*, 1952, **74**, 227) and to allow the thorium and tellurium to react; 600° was found to be the optimum temperature. After a few hours the temperature was raised to the annealing temperature. Up to the composition of $ThTe_2$, where the tellurium was rapidly absorbed by the thorium, it was convenient to seal and draw off the thorium limb at constriction *A* before the annealing. The bombs were opened *in vacuo* to prevent oxidation of the specimens, which in certain cases, for instance when the particle size was small, took place readily in air at room temperature.

FIG. 1.

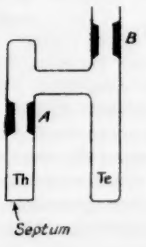
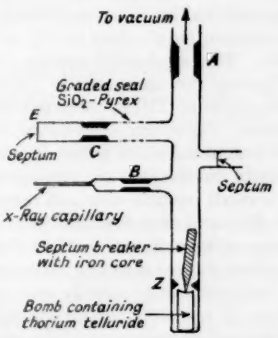


FIG. 2.



Samples were taken for *X*-ray examination and reannealing by use of the apparatus shown in Fig. 2. The bomb containing the telluride was placed in the Pyrex tube and located by the indentations *Z*. The septum breaker containing an iron core was carefully loaded into the tube and allowed to rest on the septum. Attached to the tube were *X*-ray capillaries, silica reaction tubes, and a Pyrex side arm closed by a septum. The tube was evacuated to 10^{-5} mm. and sealed at constriction *A*. The septum of the reaction tube was then broken by raising the breaker with a magnet and allowing it to fall under gravity. The *X*-ray capillary tubes and reaction tubes could then be filled, sealed, and drawn off at *B* and *C*, respectively. If the thorium telluride had formed into lumps it was first transferred under vacuum to a flask, containing a glass ball, where it could be ball-milled to a powder. It was then loaded into the *X*-ray and reaction tubes, *in vacuo*, as above.

The H-apparatus was also used for the determination of the upper limit of tellurium composition in the system. Thorium and tellurium in the ratio 1 : 5 were placed in separate limbs of the apparatus, which was evacuated to 10^{-5} mm., sealed, and placed in an oven at 600°. The tellurium limb was kept at a slightly lower temperature (~10°) than the thorium limb, making it impossible for free tellurium to remain in the latter. After being heated for a week the apparatus was cooled, the tellurium limb being always kept at a lower temperature than the thorium limb. It was then sealed at constriction *A*, and the thorium limb drawn off. The tellurium limb was cut open and weighed, the tellurium dissolved out in concentrated sulphuric acid, and the glass sections washed, dried, and weighed. Thus the weight of tellurium remaining in the limb could be directly determined and, the mass of the starting material being known, the composition of the telluride could be readily calculated. From phase-rule considerations, it being assumed that the dissociation pressure of the highest telluride, is less than the vapour pressure of tellurium at approximately the same temperature and that thermodynamic

equilibrium had been attained, the telluride formed must be the highest possible and will also be pure. From a series of such experiments the upper limit of tellurium content was found to correspond to $ThTe_{2\cdot66}$ (Th_3Te_8). Identical experiments in the thorium–selenium system gave an upper limit of $ThSe_{2\cdot33}$ (Th_3Se_7). The latter result had also been obtained by other methods (D'Eye *et al.*, *loc. cit.*).

After the upper limit had been determined as $ThTe_{2\cdot66}$, the H-apparatus was used to determine the composition of the next lower telluride. The lower limit had been unambiguously determined as ThTe and it further appeared from the *X*-ray studies that there was only one intermediate telluride, probably $ThTe_2$. Accordingly ThTe and $ThTe_{2\cdot66}$ were prepared in equivalent amounts in reaction tubes with the septum type end. These tubes together with septum breakers were loaded into separate limbs of an H-apparatus which was evacuated and sealed. The glass septa were broken, and the breakers withdrawn into the upper section of the apparatus which was then placed in a furnace and annealed for a week at 800°. Samples were next taken from each limb for *X*-ray and chemical analysis. From phase-rule considerations, if we assume that the highest telluride has a higher dissociation pressure than the next lower telluride, then the former will be degraded to the latter, where degradation will stop :

$$ThTe_{2\cdot66} \longrightarrow ThTe_x + (2\cdot66 - x)Te : \text{ dissociation pressure, } u \text{ mm.}$$
$$ThTe_x \rightleftharpoons ThTe + (x - 1)Te : \quad \text{,,} \quad \text{,,} \quad v \text{ mm.}$$

At equilibrium the system will be invariant at constant temperature, with two solid phases and one gas phase present. The $ThTe_{2\cdot66}$ limb should now contain pure $ThTe_x$, and the other limb a mixture of $ThTe_x$ and ThTe. The analytical data gave $x = 1\cdot94$. The thorium used contained about 0·5% of oxygen (equivalent to 5% of ThO_2) so it would be expected that some ThOTe would be formed. The analytical results are therefore in fair agreement with the intermediate telluride's having the composition $ThTe_2$. *X*-Ray photographs of the $ThTe_{1\cdot94}$ were identical with photographs of $ThTe_2$ prepared by direct union.

(ii) *Thorium oxytelluride.* Thorium, tellurium, and thorium dioxide in the requisite quantities were heated in evacuated silica tubes at 1100° overnight. The dioxide was prepared by heating thorium oxalate in a slow air stream at 400° (D'Eye and Sellman, A.E.R.E. C/R 1286); it then had a small particle size and reacts more readily than samples prepared at higher temperatures. *X*-Ray and chemical analysis showed the resulting product to be ThOTe.

(b) *Tensimetric Studies.*—One classical method for the determination of the phases present in a two-component system is to measure dissociation pressures in that system as the composition is varied. This method is usually only applicable where the pressures are greater than a few mm. However, if a quartz helix-type balance is used, it should, in certain cases, be possible to measure dissociation pressures of the order of 10^{-6} mm. from the absolute evaporation rate, in the same way as done by Langmuir and others for metals of low vapour pressure. If the loss of weight from a known surface area of metal is measured (Marshall, *J. Amer. Chem. Soc.*, 1937, **59**, 1161) then the vapour pressure can be readily calculated from the expression $\mu = \alpha P(M/2\pi RT)^{\frac{1}{2}}$, where μ is the weight loss per unit area per unit time, α is the accommodation coefficient, P the vapour pressure, M the molecular weight, and T the absolute temperature. Thus $\mu = KP$, where K is a constant and is equal to $\alpha(M/2\pi RT)^{\frac{1}{2}}$. For convenience, therefore, the rate μ can be plotted directly against composition. The rate and hence the pressure will be constant when the system is univariant. Horizontal curves must indicate regions in which two solid phases are present. Breaks in the curves will necessarily indicate the compositions of the various phases present in the system. Accordingly to test the practicability of this technique the known nickel–sulphur system was investigated. The results obtained were in excellent agreement with data from other experimental sources (D'Eye and Sellman, A.E.R.E. C/R 1077). The method, having proved practicable for this system, was tried for thorium–tellurium. With nickel–sulphur the sample was in the form of a thin sheet with a high surface area : unit mass ratio. It was not possible to obtain thin foils of thorium and hence of thorium telluride owing to the inherent difficulties of preparation. $ThTe_3$ in powder form was therefore loaded into a glass bucket of negligible weight. A run temperature of 300° gave the requisite rate of evaporation. The surface area of the sample was unknown in this case and an assumption was made that it would remain approximately constant. Thus instead of plotting μ [$= (1/A)(dw/dt) = KP$] against composition, dw/dt was plotted.

The results obtained with this system could not be as unequivocal as those for the nickel–sulphur system, for in this case the rate of evaporation, instead of being controlled solely by the true dissociation pressure, is also necessarily controlled by the rate of diffusion of tellurium through a layer of dissociated material owing to the sample's being in powder form. However

the breaks in the resulting curves gave positive indications of $ThTe_{2\cdot66}$ and $ThTe_2$. No break was observed in the region $ThTe_2$–ThTe, indicating that no intermediate telluride, such as Th_2Te_3, existed.

(c) X-*Ray Analysis.*—Samples were finely ground and loaded into thin-walled Pyrex capillaries of about 0·3 mm. in diameter. Powder-diffraction photographs were taken with use of standard *X*-ray equipment, 9- and 19-cm. Unicam cameras, and filtered Cu-$K\alpha$ radiation. The intensities of the lines on the resulting photographs were estimated visually.

(d) *Chemical Analysis.*—(i) The gross composition of the samples was determined by ignition in air and weighing as thorium dioxide, tellurium being determined by difference.

(ii) For complete analysis the tellurides were leached from the sample with concentrated nitric acid at about 30°, thus leaving behind any thorium or thorium dioxide. The sample was first covered with water before addition of the acid to prevent the extremely vigorous initial reaction. The thorium and tellurium were then determined by conversion into thorium dioxide and metal, respectively. Satisfactorily reproducible results were obtained. Method (ii) proved particularly useful especially in the two-phase region, thorium/tellurium > 1, where thorium is one of the phases present.

The solution of the telluride in nitric acid, after separation of any residue, was carefully evaporated to dryness on a water-bath and then taken up in dilute hydrochloric acid (*ca.* 3N). The tellurium was precipitated by adding a saturated solution of sulphur dioxide and 10% hydrazine hydrochloride solution. In order to coagulate the precipitate the solution was boiled for a few minutes. The tellurium was then filtered off, washed with water, dried at 110°, and weighed. The thorium in the filtrate was determined by precipitation as the oxalate and ignition to the dioxide.

Results and Discussion

In the region where the thorium : tellurium ratio was greater than unity two phases were observed from the *X*-ray diffraction studies, *viz.*, thorium and a phase with a primitive cubic cell. Photographs of a sample of gross composition ThTe, which had been heated overnight at 900° in silica bombs as described above, were identical with those of this cubic phase.

The phase ThTe possessed the cæsium chloride-type structure with $a = 3{\cdot}819$ *kX*. No solid solution range was observed, but owing to the rather poor *X*-ray diffraction photographs, small variations of the cell dimension would not have been observed. ThTe is black, and is degraded to its constituents when heated *in vacuo*, degradation starting in the region of 500°. It is therefore not isostructural with ThSe which has the face-centred cubic sodium chloride-type structure with $a = 5{\cdot}862$ *kX* and exists over a small solid-solution range from $ThSe_{0\cdot95}$ to $ThSe_{1\cdot1}$. Further, it differs from ThSe in that ThSe melts without degradation at 1880° and is gold-coloured. No compound was found below ThTe, which is therefore the lower limiting phase in the system.

Above ThTe, in the region $1 <$ tellurium : thorium < 2, two phases were again observed : ThTe and a new phase. Photographs of the new phase were identical with those of $ThTe_2$ prepared both by direct union of the elements and by the degradation of $ThTe_{2\cdot66}$ in an H-apparatus. It appears from these results and from the tensimetric studies that no intermediate telluride such as Th_2Te_3 is formed. This is in direct contrast with the thorium–selenium and the thorium–sulphur system where the compounds Th_2X_3 and Th_7X_{12} (where X = S or Se) are found which all melt without degradation above 1460°.

The upper limiting composition of the system was readily found, by using the H-apparatus, to be $ThTe_{2\cdot66}$. This gave complex *X*-ray diffraction photographs. The upper limit in the thorium–selenium system (D'Eye, Sellman, and Murray, *loc. cit.*) was $ThSe_{2\cdot33}$. This also had a low symmetry, giving complex photographs. Both $ThTe_{2\cdot66}$ and $ThSe_{2\cdot33}$ are readily degraded when heated *in vacuo* to the next lowest compound ThX_2 (X = Se or Te).

The method of tensimetric degradation of a sample of gross composition $ThTe_3$, a silica spring balance being used, also gave a positive indication of the existence of $ThTe_{2\cdot66}$ as the upper limiting phase.

The composition of the next lower telluride was determined by three principal methods. The tensimetric degradation of $ThTe_3$ showed a break in the resulting graph at $ThTe_2$.

Also *X*-ray photographs of $ThTe_2$, prepared by direct union of the elements, showed only one phase and were identical with photographs of $ThTe_2$ prepared by use of the H-apparatus. $ThTe_2$ gave poor *X*-ray diffraction photographs which were dissimilar from photographs of $ThSe_2$. Both $ThSe_2$ and $ThTe_2$ show the common property of degradation to lower compounds when heated *in vacuo*, in contrast to ThS_2 which melts unchanged at 1905°.

The oxytelluride ThOTe gave good *X*-ray photographs and is isostructural with ThOSe and ThOS. ThOTe is degraded when heated *in vacuo* into its constituents thorium dioxide, thorium, and tellurium, whereas ThOSe melts without degradation at 2200°.

The thorium selenides were found to be isostructural with the thorium sulphides. The m. p.s of the selenides were invariably lower than those of the corresponding sulphides as can be seen from the following table:

ThS	>2200°	$ThS_{1\cdot5}$	1950°	$ThS_{1\cdot7}$	1770°	ThS_2	1905°
ThSe	1880	$ThSe_{1\cdot5}$	1490	$ThSe_{1\cdot7}$	1460	$ThSe_2$	(degraded before melting)

It is seen that $ThSe_2$ is degraded when heated at 1000°, in contrast to ThS_2 which melts at 1905°. It appears that the increase in size of the anions causes the selenides to be slightly less stable than the sulphides. The effect is more marked in the case of the tellurides, which are all degraded when heated *in vacuo* well below 1000°. With the tellurides also the increase in size of the anion appears to cause structural changes, as only the oxytelluride is isostructural with its corresponding selenide and sulphide.

X-Ray Crystallographic Data.—The powders for *X*-ray analysis were of small particle size owing to the impractability of melting them on account of degradation. Thus the diffraction photographs were invariably of rather poor quality. This fact, together with the fact that both $ThTe_2$ and $ThTe_{2\cdot66}$ appear to have a fairly low symmetry, has prevented complete crystal structure analyses being carried out. However, both ThTe and ThOTe are of higher symmetry, and complete crystal structures have been obtained.

(*a*) ThTe. From a consideration of the values of $\sin^2\theta$ it appeared that the structure possessed cubic symmetry. The diffraction pattern was successfully indexed on this basis, and from a Nelson–Riley extrapolation (*Proc. Phys. Soc.*, 1945, **57**, 160) to $\theta = 90°$ the cell constant was found to be $a = 3{\cdot}819 \pm 0{\cdot}002$ *kX*. With one molecule per unit cell the calculated density is $\rho_c = 10{\cdot}63$ g./c.c. The absences in the observed indices of the reflections seem to indicate body-centred cubic symmetry. On further consideration this is unlikely with only one molecule of the ThTe per unit cell, as the body-centred space-groups require like atoms to be placed on a 2-fold position (000; 1/2, 1/2, 1/2). This would permit a minimum of two like atoms per unit cell. If, however, the thorium atoms were at the corners and the tellurium atoms at the body centres of the cells it might well be expected that tellurium, with an atomic number of 52, when scattering completely out of phase with thorium (atomic number 90) would cause the reflections where $h + k + l = 2n + 1$ to be extremely weak. Thus, these reflections might well not be observed on the photographs on account of the inherently high background due to white radiation. This was later shown to be the case.

Accordingly, thorium and tellurium were placed on the 1(*a*) and 1(*b*) special positions respectively in the primitive cubic space-group $O_h^1 - Pm3m$ (CsCl-type structure). The calculated intensities I_c, where $I_c \propto F^2 p\ (1 + \cos^2 2\theta)/\sin^2\theta \cos\theta$ (where F is the structure factor, p the multiplicity constant, and the function of θ is the Lorentz correction factor), are seen from the following table to be in good agreement with the observed intensities I_o.

hkl	$\sin^2\theta$, obs.	$\sin^2\theta$, calc.	I_o	I_c	*hkl*	$\sin^2\theta$, obs.	$\sin^2\theta$, calc.	I_o	I_c
100	—	0·0406	—	9·0	310	0·4065	0·4058	w	15·9
110	0·0814	0·0812	s	100·0	311	—	0·4464	—	1·3
111	—	0·1217	—	3·2	222	0·4878	0·4870	vvw	4·3
200	0·1627	0·1623	w	18·3	320	—	0·5275	—	1·1
210	—	0·2029	—	4·2	321	0·5686	0·5681	m	21·4
211	0·2437	0·2435	m	36·5	400	very	0·6493	diffuse	2·7
220	0·3249	0·3246	w	11·3		diffuse			
300 } 221 }	—	0·3652	—	2·3					

Each thorium atom will now be surrounded by eight tellurium atoms with a thorium–tellurium distance of 3·31 *kX*. It would appear that ThTe, like ThSe and ThS, is not wholly ionic in character. It is probable that the increase in size of the anion in the compounds ThS, ThSe, and ThTe gives rise to the transition from the face-centred cubic arrangement of ThS (Zachariasen, *loc. cit.*) and ThSe (D'Eye *et al.*, *loc. cit.*) to the primitive cubic structure of ThTe (cæsium chloride-type structure).

(*b*) ThOTe. The samples of ThOTe were diluted with gum tragacanth before being loaded into the thin-walled Pyrex capillaries. The dilution with gum tragacanth increases the absorption factor $A : I' = IA$, where I and I' are the true and observed intensities respectively, so that the low-angle diffraction lines are increased in intensity.

For the undiluted ThOTe the values of A for various values of θ can be calculated from the expression $A = \alpha(\theta)/\mu\rho r$, where μ is the mass coefficient of absorption, ρ the density, and r the radius of the specimen in cm. This expression can only be used when the value of $\mu\rho r$ is high (>5). Values of $\alpha(\theta)$ can be obtained from a graph of $\alpha(\theta)$ against θ (Classen, *Phil. Mag.*, 1930, **9**, 60) :

$\theta°$	0	22·5	45	67·5	90
$100A$	0	0·09	0·34	0·68	0·92

In order to increase these values of A it is obviously necessary to reduce the value of $\mu\rho r$. It is not possible to reduce r sufficiently to affect A ; therefore the density ρ of the sample must be reduced. In the simple case of a rod of square base a, the diffracted intensity I' for $\theta = 0$ is given by the expression $I' = I \exp(-\mu\rho a)$. The optimum value of $\mu\rho a$ is unity, and thus the ratio of the transmitted to the primary beam should be $e^{-1} = 0{\cdot}37$ (Guinier, " X-ray Crystallographic Technology," Hilger–Watts Ltd., 1952). Therefore very approximately in the present case $\mu\rho r$ should equal unity, giving a value for the most advantageous density ρ' of 0·22 (approx. $\rho/50$). Thus the mixture with gum tragacanth must contain about 2% of the ThOTe. With the apparent density of 0·22 the values of A are increased to the following values :

$\theta°$	0	22·5	45	67·5	90
$100A$	19·9	20·9	24·2	27·2	29·4

(" Internationale Tabellen," Vol. II, p. 584.)

By using the mathematical methods of Hesse (*Acta Cryst.*, 1948, **1**, 200) and Henry, Lipson, and Wooster (" Interpretation of *X*-Ray Diffraction Photographs," Macmillan, 1951) the diffraction pattern was successfully indexed on the basis of a tetragonal lattice with $a = 4{\cdot}112 \pm 0{\cdot}005$ and $c = 9{\cdot}544 \pm 0{\cdot}005$ *kX*. From the following table it is seen that the agreement between calculated and observed values of $\sin^2\theta$ is good. The number of molecules per unit cell is 2, giving a calculated density of 9·72 g./c.c.

The characteristic absences in the observed indices of the reflections, *hk*0 absent when $h + k \neq 2n$, indicate a space-group $D_{4h}^{7} - P4/nmm$, with the thorium and tellurium atoms on the 2(*c*) special position and the oxygen on the 2(*a*) special position (" International Tables for *X*-Ray Crystallography," Vol. 1). The values for the variable parameter for the thorium and tellurium atoms are respectively $\gamma_{Th} = 0{\cdot}18$ and $\gamma_{Te} = 0{\cdot}65$. These values were obtained by comparing the observed with the calculated intensities for the most sensitive planes. By using these parameter values the intensities I_c of all planes were calculated and their agreement with the observed values is seen from the following table to be fairly good :

hkl	$\sin^2\theta$, obs.	$\sin^2\theta$, calc.	I_o	I_c	*hkl*	$\sin^2\theta$, obs.	$\sin^2\theta$, calc.	I_o	I_c
002	0·0419	0·0416	w	21·4	004	0·1668	0·1664	vvw	2·0
101	0·0455	0·0454	m	24·5	202	0·1816	0·1816	vw	10·8
110	0·0700	0·0700	m+	81·4	211	0·1849	0·1854	vw	7·4
102	0·0768	0·0766	s	100·0	104	0·2018	0·2014	m	24·6
111	—	0·0804	—	0·05	212	0·2164	0·2166	s	41·9
003	0·0941	0·0936	vvw	2·2	203	—	0·2336	—	2·4
112	0·1117	0·1116	w	23·3	114	0·2363	0·2364	w	4·0
103	0·1291	0·1286	vvw	5·0	005	0·2607	0·2600	vvw	1·6
200	0·1403	0·1400	w+	29·3	213	0·2692	0·2686	vvw	2·8
201	0·1508	0·1504	vvw	0·2	220	0·2792	0·2800	w	10·1
113	0·1637	0·1636	vw	4·4					

The thorium–tellurium distances can now be calculated as being Th–4Te = 3·18, Th–Te = 3·55, and Th–Te = 4·00 *kX*, with a second nearest neighbour distance of Th–4Te = 5·43 *kX*. The Th–O distance is Th–4O = 2·46 *kX*. The Th–4Te distance of 3·18 *kX* is in fair agreement with the radius sum for the thorium and tellurium atoms, from Pauling's data for ionic radii ("Internationale Tabellen," Vol. II), which is 3·23 *kX*.

It would appear from the above crystallographic data that ThOTe is isostructural with ThOS and ThOSe.

Conclusion.—From *X*-ray and chemical analysis, phase-rule considerations, and tensimetric studies the compounds ThTe, $ThTe_2$, $ThTe_{2\cdot66}$, and ThOTe have been identified. Complete crystal-structure data were obtained for ThOTe and ThTe. The former was tetragonal and isostructural with ThOSe and ThOS, and the latter simple cubic with the cæsium chloride-type structure. It was not isostructural with ThSe and ThS which possess the sodium chloride-type structure. The structures of the phases $ThTe_2$ and $ThTe_{2\cdot66}$ have not been determined owing to their apparent low symmetry.

The thorium–tellurium system is not analogous to the thorium–sulphur and the thorium–selenium system. For instance: (i) No telluride corresponding to Th_2X_3, Th_7X_{12}, or $ThX_{2\cdot33}$ (where X = S or Se) was identified. (ii) The compounds ThTe, $ThTe_2$, $ThTe_{2\cdot66}$, and ThOTe are all degraded well below 1000° when heated *in vacuo*, in contrast with the selenides and sulphides which, apart from $ThX_{2\cdot33}$ (X = S or Se) and $ThSe_2$, all melt above 1460° without decomposition *in vacuo*. (iii) A telluride $ThTe_{2\cdot66}$ was found which has no analogue in the Th–S and the Th–Se system. (iv) ThTe and $ThTe_2$ are not isostructural with their corresponding sulphides and selenides.

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Cationic Polymerisation of 2 : 3-*Dihydrofurans.*

By D. A. Barr and J. B. Rose.

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The cationic polymerisation of three 2 : 3-dihydrofurans to polymers of high molecular weight is described. An investigation of the structures of the polymers is reported, and the softening-points of the polymers, which are considerably higher than those of aliphatic polyvinyl ethers, discussed in terms of their structures.

It is known (Hamann, *Angew. Chem.*, 1951, 231) that certain linear polyethers can be obtained by polymerisation of the corresponding cyclic ethers, for instance, a polymer having the repeat unit $\cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot O \cdot$ is obtained by the cationic polymerisation of tetrahydrofuran (*idem, loc. cit.*). An attempt has been made to extend this method to the preparation of polyethers, having double bonds in the chain, by the cationic polymerisation of dihydrofurans. It was found that, although 2 : 5-dihydrofurans would not polymerise, 2 : 3-dihydrofurans polymerised readily in the presence of Friedel–Crafts catalysts.

2 : 3-Dihydro-5-methylfuran polymerised on addition of catalytic quantities of boron trifluoride, the experimental method being such that water was excluded as far as possible from the system. Polymerisation took place readily at −80° to give a glass-like polymer of high molecular weight. The molecular weight of the polymer (as indicated by its intrinsic viscosity) prepared in this manner showed no regular variation with the concentration of catalyst used, but was decreased considerably by the addition of small quantities of water. These effects are illustrated in the annexed table. It appears

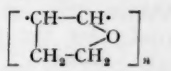
Bulk polymerisation of 2 : 3-*dihydro*-5-*methylfuran* at −80°.

[BF_3], mole $l.^{-1}$	0·01	0·01	0·033	0·10	0·01	0·01
[Added water], mole $l.^{-1}$	None	None	None	None	0·005	0·025
[η], decilitre $g.^{-1}$	5·8	7·2	7·0	5·0	0·92	0·38

that water is an effective chain-termination or transfer agent and, if polymerisation is assumed to proceed *via* carbonium ions, this behaviour is consistent with reaction of the growing chain with water either by an elimination process to give a terminal double bond or by substitution to give a terminal hydroxyl group. The addition of relatively large quantities of water to the polymerisation mixture inactivated the catalyst. Thus, when the concentration of added water was increased to 0·1 mole $l.^{-1}$ polymerisation did not take place at −80°, but set in when the polymerisation mixture was warmed to 0°. When the concentration of water was increased to 0·2 mole $l.^{-1}$ polymerisation would not take place at all. Polymerisations at −40° and at 0° gave deeply coloured products from which polymers of low molecular weight were isolated.

Polymers of high molecular weight of 2 : 3-dihydro- and of 2 : 3-dihydro-2 : 2-dimethyl-furan were prepared by polymerisation of the dry monomers at −80°, 0·01M-boron trifluoride being used as catalyst. Polymers of low molecular weight were formed when polymerisation was at room temperature or when the monomers were not carefully dried. It therefore appears that the conditions principally necessary for the preparation of polymers of high molecular weight from 2 : 3-dihydrofurans are dry monomers and low temperatures of polymerisation.

There are two types of structure possible each corresponding to one of the two modes of cationic polymerisation that appear possible for 2 : 3-dihydrofurans :

(I) $[CH_2{\cdot}CH_2{\cdot}CH{:}CH{\cdot}O{\cdot}]_n$  (II)

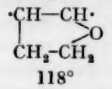
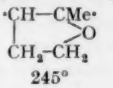
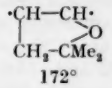
Results of an examination of the infra-red absorption spectra of the monomers and their polymers, carried out by Mr. R. G. J. Miller, are summarised in the following Table :

Frequencies (cm.$^{-1}$) of bands in infra-red absorption spectra of 2 : 3-dihydrofurans and their polymers.

	2 : 3-Dihydro-		2 : 3-Dihydro-5-methyl-		2 : 3-Dihydro--2 : 2-dimethyl-	
Furan :	monomer	polymer	monomer	polymer	monomer	polymer
C–O–C stretching	915	925	890	—	885	895
	1055	1060	1010	1060	1060	1048
cis-C=C hydrogen deformation ...	710	—	720	—	707	—
C=C stretching	1610	—	1670	—	1615	—

These data show that the absorption bands characteristic of the C=C-bond, which are present in the spectra of the monomers, do not occur in the polymers. Further, in the spectra of the polymers the bands associated with the C–O–C-frequencies occur in positions similar to those in which the ether bands of the monomers were found, and are characteristic of cyclic ethers, *e.g.*, tetrahydrofuran, which has absorption bands at 905 and 1075 $cm.^{-1}$ (H. A. Willis, personal communication), rather than of linear ethers which absorb in the region of 1130 $cm.^{-1}$, *e.g.*, polytetrahydrofuran absorbs at 1130 $cm.^{-1}$ (H. A. Willis, *loc. cit.*). This evidence is therefore completely consistent with structure (II), but inconsistent with (I). It is perhaps noteworthy that 2 : 3-dihydrofurans do not contain the group $>C{=}CH_2$, which has been considered (Schildknecht, Zoss, and Grosser, *Ind. Eng. Chem.*, 1949, **41**, 2891) to be necessary if a vinyl monomer is to form homopolymers readily by ethenoid polymerisation.

Softening-point determinations, carried out on samples of each polymer by the " Vicat " method (see " Kunstharzpressstoffe," W Mehdorn, V.D.I., Forschungs-heft VDI-Verlag G.m.b.H., Berlin, 1934), gave the values listed below. These values are considerably higher

Polymer of	2 : 3-dihydrofuran	2 : 3-dihydro-5-methylfuran	2 : 3-dihydro-2 : 2-dimethylfuran
Repeat unit			
Softening point ...	118°	245°	172°

than those of aliphatic polyvinyl ethers, which are rubbers at room temperature (Schildknecht *et al.*, *loc. cit.*). Frith and Tucket (" Linear Polymers," Longmans,

Green and Co., London, 1951, p. 328) have show that the " Vicat " softening point provides a measure of the elastic, rather than the viscous, properties of an amorphous polymer, and therefore a measure of its chain flexibility. Some explanation of the high softening point of poly-2 : 3-dihydrofuran is therefore possible on a structural basis, for in this polymer rotation about some chain bonds is prevented by their incorporation in a strained ring, while rotation about others is restricted by the steric hindrance afforded by the rings, so that the polymer chain must be less flexible than the chain in polyvinyl ethers. Construction of Stuart molecular models showed that methyl substitution on the poly-2 : 3-dihydrofuran chain increased its rigidity, while dimethyl substitution remote from the chain had a similar, though less marked, effect.

Experimental

Preparation of the Monomers.—2 : 3-Dihydrofuran was prepared by Normant's method (*Compt. rend.*, 1949, **228**, 102), and 2 : 3-dihydro-5-methylfuran according to Paul and Tchelitcheff (*Bull. Soc. chim.*, 1950, 520). A mixture of the two isomeric dihydro-2 : 2-dimethylfurans was prepared as described by Colonge and Garnier (*ibid.*, 1948, 432), and fractionated through a 3-ft. column filled with metal packing (Dixon, *J. Soc. Chem. Ind.*, 1949, **68**, 299), to give two main fractions; 2 : 3-dihydro-2 : 2-dimethylfuran, b. p. 78·0°/764 mm., n_D^{20} 1·4123 (Found : C, 73·3; H, 10·3. Calc. for $C_6H_{10}O$: C, 73·5; H, 10·3%), and 2 : 5-dihydro-2 : 2-dimethylfuran, b. p. 84·6°/764 mm., n_D^{20} 1·4158 (Found : C, 73·2; H, 10·5%). Normant (*Compt. rend.*, 1948, **227**, 283) records b. p. 77—78° for the 2 : 3-dihydrofuran, and b. p. 85—86° for its 2 : 5-isomer.

Purification of the Monomers.—2 : 3-Dihydrofurans are oxidised by air (Paul and Tchelitcheff, *loc. cit.*) to products which give characteristic infra-red absorption bands at 1728 and 1745 cm.$^{-1}$. These impurities were removed by refluxing the monomers with freshly fused potassium hydroxide, distilling then from the potash, and fractionating the distillate. To prevent further oxidation (the infra-red absorption bands rapidly reappeared if the monomers were exposed to air), the above operations were carried out under nitrogen. After fractionation, the monomers were dried *in vacuo* over sodium wire, and then distilled in a good vacuum into the storage section of the polymerisation apparatus. The purified monomers either did not absorb, or only absorbed very weakly at 1725 and 1745 cm.$^{-1}$, and had the following physical constants : 2 : 3-dihydrofuran, b. p. 54·6°/764 mm., n_D^{20} 1·4230 (Normant, *Compt. rend.*, 1949, **228**, 102, records b. p. 54·5°/760 mm., $n_D^{18·5}$ 1·424); 2 : 3-dihydro-5-methylfuran, b. p. 79·6—79·7°/760 mm., n_D^{20} 1·4296 (Schniepp and Gellar, *J. Amer. Chem. Soc.*, 1947, **69**, 672, record b. p. 80°/760 mm., n_D^{25} 1·4290); and 2 : 3-dihydro-2 : 2-dimethylfuran, b. p. 78·0°/764 mm., n_D^{20} 1·4123.

Boron Trifluoride.—This was prepared by dropping redistilled fluorosulphonic acid on to a slight excess of boric acid, and the trifluoride purified by passing it through traps cooled to −80°. The purified gas was collected in a trap cooled in liquid nitrogen, and then distilled in a nitrogen atmosphere into a second trap forming part of the polymerisation apparatus. The second trap was evacuated and the boron trifluoride melted down, out-gassed, and distilled *in vacuo*, a middle fraction being collected in a storage bulb.

Polymerisation Technique.—To exclude moisture the monomer and the catalyst were handled *in vacuo*, according to the following procedure : (i) A measured quantity of monomer was distilled into a graduated tube, and from there into the reaction tube (about 15 ml. capacity), which was constricted just below its junction with the rest of the apparatus. The monomer was then frozen by liquid nitrogen. (ii) A quantity of boron trifluoride was measured into a constant-volume, variable-pressure gas-burette, and distilled from the burette bulb on to the frozen monomer. (iii) The reaction tube was sealed, and warmed to −80° by shaking in a solid carbon dioxide–methanol bath. When polymerisation was complete (after 48 hr. at −80°) the tube was cooled with liquid nitrogen, the polymer cracking away from the glass and bursting the tube. The polymer was kept cold with liquid nitrogen and broken up in a percussion mortar. The frozen fragments were dropped into chloroform (600 ml.)–methanol (30 ml.), cooled to −60°. Ammonia was passed in and the mixture allowed to warm gradually to room temperature. The viscous solution was filtered, and the polymer recovered by precipitation with methanol. After being washed twice with methanol, the precipitated polymer was dried in a vacuum desiccator. The above procedure was necessary since, when the polymer was allowed to warm from −80° before it had been treated to destroy the catalyst, a short exothermic reaction set in and the polymer became deeply coloured, and then decomposed at 100°.

Viscosity Measurements.—The intrinsic viscosities of the polymers in chloroform solution were measured at 20°, an Ostwald No. 1 viscometer being used. The plot of η_{sp}/C against C, where η_{sp} is the specific viscosity and C the concentration, gave straight lines in the concentration range 0·025—0·15 g. decilitre^{-1}.

Softening-point Measurements.—Samples of each polymer suitable for softening-point determination were prepared by moulding the powdered polymer at 200° for 30 min. at 1000 lb./sq. in., air being excluded. In this way slightly coloured sheets of polymer were obtained, the softening points of which were determined: The specimen was stressed by a circular penetrometer needle of 1 mm.^{2} cross-sectional area loaded with 1 kg. and was heated at 50°/hr. The Vicat and 1/10 Vicat softening points are the temperatures at which penetrations of 1 mm. and 0·1 mm., respectively, are obtained.

Softening-point data.

Polymer of	$[\eta]$ (decilitre g.$^{-1}$) Before moulding	After moulding	1/10 Vicat	Vicat
2 : 3-Dihydrofuran	3·5	2·1	108°	117°
,,	2·2	1·4	107	118
2 : 3-Dihydro-5-methylfuran	6·8	4·5	238	245
,, ,,	4·2	2·5	231	245
,, ,,	0·92	1·0	>220 [a]	>220 [a]
2 : 3-Dihydro-2 : 2-dimethylfuran	8·0	3·3	162	172

[a] Determination prevented by breakdown of the apparatus at 220°.

The moulding process reduces the intrinsic viscosity of the polymer, but comparison of the data given for samples of the same polymer but of different molecular weight shows that the softening point is independent of the molecular weight, in the molecular-weight range investigated. Hence the softening points of the mouldings are a true measure of the softening points of the polymers, and are not distorted by the reduction in molecular weight caused by moulding.

The authors thank Mr. C. E. Stevenson for measuring the softening points of the polymers, and Messrs. J. Gray and M. Cudby for experimental assistance.

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Physicochemical Studies on Starches. Part I. The Characterization of the Starch present in the Seeds of the Rubber Tree, Hevea brasiliensis.

By C. T. Greenwood and J. S. M. Robertson.

[Reprint Order No. 5429.]

The starch present in the endosperm of the seeds of the rubber tree, *Hevea brasiliensis*, is intimately associated with protein. Potentiometric iodine titrations on the purified material indicated that it contained 20% of amylose. Amylopectin (containing only 0·4—0·7% of amylose) and pure amylose fractions were obtained by fractionation of the starch with thymol followed by butan-1-ol. The average length of unit chain in the amylopectin was shown to be 23 ± 1 glucose residues by both methylation and periodate oxidation studies. The latter also indicated that the majority of interchain linkages were of the 1 : 6-type. Osmotic pressure measurements, on the acetylated derivative of the amylopectin in chloroform solution, indicated a molecular weight of about $1{\cdot}8 \times 10^6$ (*ca.* 6000 glucose residues). The acetylated amylose, prepared by a method involving the minimum of degradation, was shown similarly to possess a molecular weight of $4{\cdot}4 \times 10^5$ (*ca.* 1500 glucose residues). Measurements of the limiting viscosity number of both the free and the acetylated components were also carried out.

Starch occurs in most seed materials, and many such sources have recently been examined. In this paper we report an investigation of the starch present in the endosperm of the seeds of the rubber tree, *Hevea brasiliensis*. It was isolated in granular form by a purely mechanical process avoiding reagents likely to cause degradation. It contained a

large amount of protein (41%), which appeared to surround the granules. A modified Sevag technique (Sevag, *Biochem. Z.*, 1934, **273**, 419) reduced this in a portion of the starch to negligible amounts under the desired mild conditions. Portions of non-granular starch were obtained by further extraction of the starch–protein residue with chloral hydrate (Meyer and Bernfeld, *Helv. Chim. Acta*, 1940, **23**, 875) and then with hot water. Protein still contaminated the resultant products and had a marked effect on their interaction with iodine. [This is of general importance in the study of starch-like materials (Anderson and Greenwood, unpublished results).] The purified starch had a maximum binding power of 3·68% of iodine by weight, which under the conditions employed corresponded to an amylose-content of 20%.

A separation of the amylose and amylopectin fractions was carried out. The most satisfactory method for preparing purified amylopectin (0·4—0·7% of amylose) involved the use of thymol as a precipitant (Haworth, Peat, and Sagrott, *Nature*, 1946, **157**, 19),

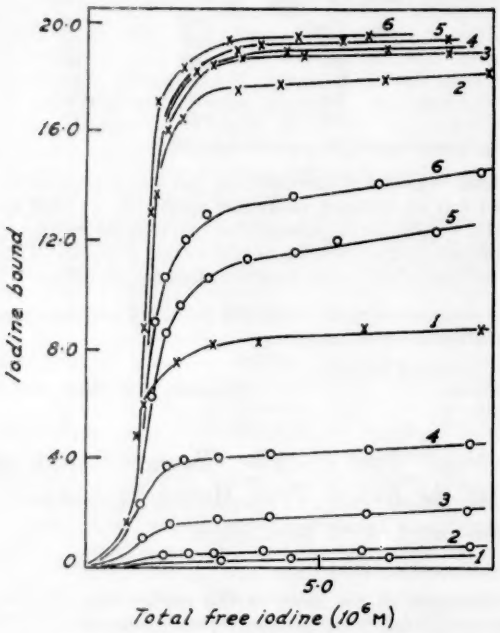

FIG. 1. *Iodine-titration curves of fractionation products.*

—— × —— *Curves for precipitates.*
—— ○ —— *Curves for material in corresponding supernatant liquor.*

1, *Thymol complex.*
2—6, *Butanol complexes* 1—5.

but yielded at the same time an impure amylose fraction (see Table 1). This fraction could then be purified *via* its butanol complex (Higginbotham and Morrison, *Shirley Inst. Mem.*, 1948, **22**, 148). To minimize inadvertent degradation of the linear component at elevated temperatures (Bottle, Gilbert, Greenwood, and Saad, *Chem. and Ind.*, 1953, 541), the fractionation was carried out as far as possible under nitrogen. Table 1 gives the results of potentiometric iodine titrations on, and measurements of the optical densities of the polysaccharide–iodine complexes (Hassid and McCready, *J. Amer. Chem. Soc.*, 1943, **65**, 1154) of, the fractionation products, in particular on material remaining in the supernatant liquors after removal of the various complexes. Amylose binding 19·2% of iodine by weight was obtained after five reprecipitations. Although it has been suggested that all amyloses possess the same maximum iodine-binding power (Higginbotham and Morrison, *loc. cit.*), recent work indicates that this may depend on the source of the amylose and the methods used for fractionation (see, *e.g.*, Schoch in Radley, " Starch and its Derivatives," Chapman & Hall, London, 1953, Vol. I, p. 123). The value will also depend on the potentiometric titration conditions ([iodide ion], [iodine], pH, and temp.). For accurate results, it appears that the only satisfactory method for estimating the percentage of

amylose in a given starch or its fractionation products involves an experimental determination of the maximum iodine-binding power of the *pure* amylose component of that starch and, if possible, the complexing reagent should be varied during this preparation. Percentages of amylose shown in Table 1 have been calculated on this basis. Fig. 1 shows the corresponding iodine titration curves. The weight of material in the supernatant liquor decreased regularly during a successful fractionation (if retrogradation occurred, the amount in the supernatant liquor increased and its properties changed). Amylopectin was obtained from the first butanol supernatant liquor, but the shape of the iodine-titration curves for subsequent supernatant liquors (Fig. 1) and the increase in the wave-length of maximum absorption of the polysaccharide–iodine complex (Table 1) suggested that after one or two re-fractionations actual molecular-weight fractionation of the amylose was occurring and short-chain amyloses were appearing in the supernatant liquors. The

TABLE 1. *Analyses of the fractionation products.*

Product		Wt. (mg.)	$\lambda_{max.}$ (Å)	Iodine affinity *	Amylose (%)
(a) *Precipitates.*					
Thymol complex		—	6000	8·3	43
Butanol complex :	1	—	—	17·4	91
	2	—	—	18·6	97
	3	—	—	18·8	98
	4	—	—	19·0	99
	5	227 †	6550	19·2 ‡	100
(b) *Material in supernatant liquors from* :					
Thymol complex		855	5500	0·14	0·7
Butanol complex :	1	230	5700	0·35	1·8
	2	30	6000	3·65	19
	3	19	—	1·70	9
	4	32	6250	10·6	55
	5	14	—	13·0	68

* Expressed as the maximum iodine binding power (%).
† A further 65 mg. were used in analyses of butanol complexes 1—4.
‡ Average of 6 determinations.

apparent molecular-weight distribution curve of the final amylose and the corresponding iodine affinity (cf. Kerr, Cleveland, and Katzbeck, *J. Amer. Chem. Soc.*, 1951, **73**, 3916) may thus depend on the method of fractionation. In this instance, 7% of the total weight of starch was present in the supernatant liquors. (This is increased to 20% if that from the first butanol complex is included.) Fractionation involving the use of thymol followed by butanol as complexing agents appears to be a general method for preparation of both pure amylose and amylopectin (Anderson and Greenwood, unpublished observations).

Methylation of the amylopectin fraction was carried out by suspending the polysaccharide in liquid ammonia and treating the suspension with sodium and methyl iodide under the conditions described by Hodge, Karjala, and Hilbert (*ibid.*, p. 3312). This method was claimed to give completely methylated starch products without severe degradation. The trimethyl derivative was treated with methanolic hydrogen chloride, and the methylated methyl glucosides obtained were hydrolysed with aqueous hydrochloric acid. Examination of the mixture of reducing sugars both on paper chromatograms and on a column of powdered cellulose showed the presence of 2 : 3 : 4 : 6-tetra-*O*-methyl-, 2 : 3 : 6-tri-*O*-methyl-, and 2 : 3-di-*O*-methyl-glucose, and a mixture of 2 : 6- and 3 : 6-di-*O*-methylglucose, which probably arose from incomplete methylation or some demethylation during hydrolysis. Only traces of mono-*O*-methylglucoses and glucose were detected. The yield of tetra-*O*-methylglucose corresponded to the presence of one non-reducing terminal group for every twenty-three glucose residues in the molecule. The value was confirmed by periodate oxidation of both the amylopectin fraction and the whole starch. It follows that the average length of unit chain in the amylopectin is 23 glucose residues, a value similar to that found in other starches (cf. Brown, Halsall, Hirst, and Jones, *J.*, 1948, 27). Further, the isolation of only 0·75% of glucose from the hydrolysis products

of the periodate-oxidized amylopectin showed that the majority (80%) of the interchain linkages were of the 1 : 6-type.

As a preliminary to determining the size of the amylopectin, the tri-*O*-acetyl derivative was prepared. Difficulty was found in carrying out this esterification with a pyridine–acetic anhydride mixture even on freeze-dried material, although various authors have claimed this to be successful (Higginbotham and Morrison, *loc. cit.*; Meyer, Bernfeld, and Hohenemser, *Helv. Chim. Acta*, 1940, **23**, 885). Potter and Hassid's method (*J. Amer. Chem. Soc.*, 1948, **70**, 3774) involving a prior dispersion in formamide was the most satisfactory. The limiting viscosity number $[\eta]$ (I.U.P.A.C. nomenclature, *J. Polymer Sci.*, 1952, **8**, 257) of the triacetate in chloroform solution was 2·33. Measurements of the osmotic pressure of the acetate in chloroform solution indicated that the number-average molecular weight ($\bar{M}_n$) was approximately 1,800,000. The π/c *versus* c curve (Fig. 2) appeared to be linear for the range of concentrations investigated (cf. Kerr, Cleveland, and Katzbeck, *J. Amer. Chem. Soc.*, 1951, **73**, 111). The molecular-weight data, in conjunction with the average length of unit chain of 23 glucose residues, showed that the amylopectin had a highly branched structure (*ca.* 260 branches per molecule). The amylopectin was also

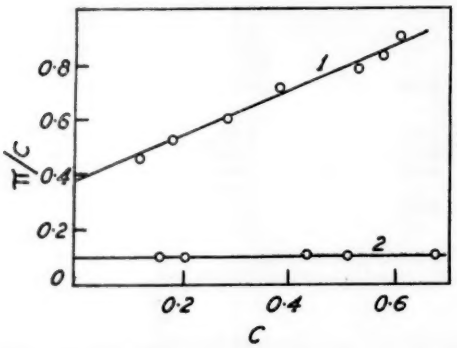

FIG. 2. *Graph of* π/c versus c *for the acetylated starch components in chloroform solution.*
1, *Amylose acetate.*
2, *Amylopectin acetate.*

characterized by measuring the limiting viscosity number of the unsubstituted component in M-potassium hydroxide (Lansky, Kooi, and Schoch, *ibid.*, 1949, **71**, 4066). For comparison, the limiting viscosity number of a sample of rabbit-liver glycogen (kindly provided by Dr. D. J. Manners) was measured in this solvent.

Methylation of the amylose was not attempted. Although other workers have isolated a small quantity of tetra-*O*-methylglucose from the hydrolysed tri-*O*-methyl derivative (see, *e.g.*, Mayer, Wertheim, and Bernfeld, *Helv. Chim. Acta*, 1940, **23**, 865; Bourne, Fantes, and Peat, *J.*, 1949, 1109; MacWilliam and Percival, *J.*, 1951, 2259), the accuracy of such an estimation is not high with limited quantities of material. In view of this, and the labile nature of the linkages in the linear molecule (Bottle, Gilbert, Greenwood, and Saad, *loc. cit.*), it appeared most satisfactory to estimate the chain length of the amylose from the molecular size of the tri-*O*-acetyl derivative, although this procedure cannot indicate whether the molecule is entirely linear (cf. Kerr and Cleveland, *J. Amer. Chem. Soc.*, 1952, **74**, 4036; Potter and Hassid, *loc. cit.*). An estimate of the degradation accompanying acetylation of amylose was obtained by measuring the limiting viscosity numbers of products isolated under different reaction conditions (see Table 3), and the method involving minimum degradation was then used for esterification. The limiting viscosity number of the product was 3·35, whilst the number-average molecular weight obtained from osmotic-pressure measurements in chloroform solution (Fig. 2) was 440,000 (*ca.* 1500 glucose residues). In M-potassium hydroxide, the limiting viscosity number for the unsubstituted amylose was 2·15.

Treatment of the amylose with crystalline sweet potato β-amylase gave 79% conversion into maltose (Dr. D. J. Manners, personal communication). The residual polysaccharide was rapidly degraded by salivary amylase and was therefore composed of α-1 : 4-linked

glucose residues. The nature of the barrier to β-amylolysis is being investigated (cf. Hopkins and Bird, *Nature*, 1953, **172**, 492; Peat and Whelan, *ibid.*, p. 494).

TABLE 2. *Molecular-weight data.*

	Amylose	Amylopectin	Glycogen
Limiting viscosity no. in M-KOH	2·15	1·02	0·10
Limiting viscosity no. of acetate	3·35	2·33	—
Molecular weight of acetate	$4{\cdot}4 \times 10^5$	$1{\cdot}8 \times 10^6$	$4{\cdot}8 \times 10^6$ *
Average degree of polymerization	1,500	6,000	30,000
Average length of unit-chain	—	23	12
Approx. number of branches per molecule	—	260	2,500

* From sedimentation measurements on unsubstituted glycogen (Greenwood and Manners, unpublished results).

The molecular-weight data are summarized in Table 2. The values are of the same order as those reported for the components from other starches (see, *e.g.*, Potter and Hassid, *loc. cit.*; Potter, Hassid, and Joslyn, *J. Amer. Chem. Soc.*, 1949, **71**, 4075; Higginbotham, *Shirley Inst. Mem.*, 1950, **24**, 221).

Although kinetic-energy corrections have been considered in obtaining the limiting viscosity numbers quoted, no correction was applied for shear effects (cf. Krigbaum and Flory, *J. Polymer Sci.*, 1953, **11**, 37). These may be considerably more important in the case of the elongated amylose component than for the branched products. Experiments are now in progress to investigate this. The large difference between the limiting viscosity numbers of the amylopectin and the glycogen samples is significant, and must be related to a fundamental difference in the molecular structure of these branched α-1 : 4-glucosans (cf. Hirst and Young, *J.*, 1939, 1471), as a result of which the amylopectin molecule must possess a more extended shape in solution than glycogen. It has been suggested recently by Hirst and Manners (*Chem. and Ind.*, 1954, 224) that this is due to the two polysaccharides' having different degrees of multiple branching.

EXPERIMENTAL

Preliminary Extraction of Oil from the Rubber Seed Endosperm.—Crushed endosperm was exhaustively extracted with benzene–methanol (1 : 1, v/v). The product was filtered, dried *in vacuo* over calcium chloride, and then ground in a hammer-mill to yield a fine buff-coloured powder (47% of the original weight of endosperm).

Isolation of Starch.—Defatted endosperm (600 g.) was extracted several times (*ca.* 24 hr. periods) by shaking it with cold water under toluene (6 l.), and the crude starch was isolated by filtering the aqueous suspension through muslin. The filtrate yielded a light brown sediment, which was washed by decantation with water and then refluxed three times with 80% aqueous methanol (30 ml./1 g.; 3 hr. periods) to ensure complete removal of fats. The yield was *ca.* 60 g. [Found: N (semi-micro Kjeldahl), 6·5%; *i.e.*, protein, 40·6%].

Removal of Protein from the Starch.—Microscopic examination indicated that contaminating protein probably formed a surface layer, as little extraneous material was visible and the granules were noticeably larger than in the purified starch (apart from the difference in size, little change in outward appearance was evident). Treatment with water at 50° did not coagulate the protein, but leached material giving a blue stain with iodine from the granule.

(a) *Treatment with toluene and butanol.* A suspension of starch in M-sodium chloride (2 g./200 ml.) was shaken with an equal volume of toluene for 6 hr. to denature the protein, and then set aside for 3 hr. to allow separation of the starch granules from the toluene–protein layer. (This procedure gave more effective separation than centrifugation at low speeds.) The brown precipitate obtained at the toluene–water interface was removed. The sedimented product consisted of two layers, the lower being mainly starch and the brown upper one mainly protein. These two layers were then each resuspended in M-sodium chloride and re-extracted with toluene as above. Combining the lower white layers, and also the upper layers, and continually re-extracting them with toluene, gave three products: (i) white starch which formed no interfacial precipitate, (ii) pale brown impure starch, and (iii) coagulated protein. Each was then suspended in M-sodium chloride (1 vol.) and shaken overnight with butanol (2·5 vols.), and

the above procedure repeated. The products, after removal of salt by repeated decantation with water, consisted of starch A (*ca.* 15 g.) (Found : N, 0·05%) and a protein-contaminated residue. Starch A was never dried and was stored under ethanol at 0°.

(b) *Extraction with chloral hydrate.* Starch in the residue could not be extracted with either (i) 1% sodium sulphite solution or (ii) 0·3% aqueous sulphur dioxide (Hilbert and McMasters, *J. Biol. Chem.*, 1946, **162**, 229) and so was extracted with chloral hydrate (Mayer and Bernfeld, *loc. cit.*), to yield starch B (5·2 g.) (Found : N, 0·41%).

(c) *Hot-water extraction.* The residue was stirred vigorously with water (2 l.) at 95° under nitrogen for 1 hr. The protein residue was removed on the centrifuge (18 g.) (Found : N, 14·4%), and the supernatant liquor yielded on freeze-drying starch C (20 g.) (Found : N, 4·9%).

Properties of Starch A.—This white powder consisted of small spherical birefringent granules (diam. 4·4 μ). In hot water it formed a clear paste which gave a deep blue colour with iodine. On hydrolysis with 2% sulphuric acid, the starch yielded 98% of the theoretical amount of glucose (quantitative chromatographic determination), and no other sugar could be detected on the paper chromatogram. This material had $[\alpha]_D^{16}$ +161° (*c*, 0·763% in N-NaOH), $[\alpha]_D$ +156° (*c*, 1·0% in 30% $HClO_4$) (Found : ash, 0·05; N, 0·05%). The optical density of the colour developed when starch (1 mg.) was stained with iodine (2 mg.) and potassium iodide (20 mg.) in distilled water (100 ml.) was measured at various wave-lengths between 4000 and 7000 Å in cells of 1 cm. length against the same iodine solution (Hassid and McCready, *loc. cit.*) by means of a Unicam spectrophotometer. For comparison with " blue values " (Bourne, Haworth, Macey, and Peat, *J.*, 1948, 924), optical densities in a 4-cm. cell at 6800 Å were calculated by assuming a linear relation between optical density and (*a*) length of cell and (*b*) concentration at this wave-length. For starch A, this density was 0·31 (the corresponding value for starch B was 0·27).

Potentiometric Iodine Titration.—The differential potentiometric titration technique of Gilbert and Marriot (*Trans. Faraday Soc.*, 1948, **44**, 84) was employed, with the electrometer described by Anderson and Greenwood (*Chem. and Ind.*, 1953, 476). The sensitivity of this electrometer enabled potentials of 0·01 mv to be measured. Titration conditions were : [iodide], 0·01M ; [starch], *ca.* 1 mg./50 ml. ; [amylose], *ca.* 1 mg./200 ml. ; [amylopectin], *ca.* 1 mg./30 ml. ; pH, 5·85 ; temp., 20°. The two half-cells were stirred automatically throughout the experiment. With careful mixing of solutions, a negligible potential difference was observed at the start of the experiment. Points on the titration curve were obtained by adding small increments of iodine to the solution cell, and then adding iodine to the control until the concentration of free iodine in each cell was equal after 2—3 min. had been allowed for equilibration. The total free iodine in the starch solution was plotted against mg. of iodine bound per 100 mg. of polysaccharide. Starch A showed a maximum binding power of 3·86%, which under the conditions used corresponded to an amylose content of 20% (see below). Starch B had a binding power of 3·02% (15·7% of amylose), which suggested that protein present interfered considerably with the iodine uptake of the starch.

Starch A was used in all further investigations.

Periodate Oxidation of the Starch.—A sample (0·469 g.) in water (80 ml.) was treated with 0·25M-sodium metaperiodate (40 ml.) and potassium chloride (5 g.) as described by Brown, Halsall, Hirst, and Jones (*J.*, 1948, 27). The yield of formic acid corresponded to 0·034 mole from 162 g. of the starch after 220 hr. (constant value), *i.e.*, 1 mole per 24 glucose residues in the amylopectin fraction. A duplicate experiment yielded 1 mole per 23 glucose residues.

Determination of Glucose Residues in the Starch linked through $C_{(1)}$, $C_{(4)}$, *and* $C_{(6)}$.—After completion of the above oxidation the solutions were freed from periodate and hydrolysed, and the percentage of glucose remaining was quantitatively estimated by MacWilliam and Percival's method (*J.*, 1951, 2259). The amount (1·2%) of glucose found indicated that 98·8% of the residues in the starch were linked through $C_{(1)}$–$C_{(4)}$ or $C_{(1)}$–$C_{(6)}$, and that, as the chain length was 24 glucose units, about 70% of the interchain linkages were of the 1 : 6-type.

Fractionation of the Starch.—The starch was defatted by refluxing it several times with methanol, and then portions were fractionated with thymol as a complexing agent (Haworth, Peat, and Sagrott, *loc. cit.*), followed by butanol (Higginbotham and Morrison, *loc. cit.*). Fractionation was carried out under nitrogen to minimise degradation of amylose (Bottle, Gilbert, Greenwood, and Saad, *loc. cit.*). The course of the fractionation was followed by potentiometric and optical measurements on the polysaccharide–iodine complexes of the precipitated material, and in addition on material in the supernatant liquors.

(a) *Fractionation I.* This will not be reported in detail. Starch (8 g.) yielded amylose I

[*ca.* 1·70 g.; O.D.$^{6800}_{4\text{ cm.}}$ (*i.e.* optical density as above) 1·00; $\lambda_{max.}$ 6250 Å; max. iodine-binding power, 15·4%], amylopectin I (4·3 g.; O.D.$^{6800}_{4\text{ cm.}}$ 0·08; $\lambda_{max.}$ 5250 Å; max. iodine-binding power, 0·07%; amylose, 0·4%), and supernatant material (1·60 g.). Improvements in methods were incorporated in fractionation II.

(*b*) *Fractionation II.* A suspension of starch (*ca.* 2 g.) in water (40 ml.) was added to vigorously stirred boiling water (260 ml.) under nitrogen, and boiling continued for 20 min. The temperature was then allowed to fall to 60°, powdered thymol (0·5 g.) was added, and the mixture stirred at 60° for 30 min., then kept at room temperature (15—17°) for 3 days to allow the thymol complex to be precipitated. The suspension was then passed three times through a Sharples supercentrifuge to remove the amylose complex as completely as possible. The clear supernatant liquor was freeze-dried, refluxed with methanol to remove thymol, redissolved, and freeze-dried again, to yield amylopectin II (1·38 g.; O.D.$^{6800}_{4\text{ cm.}}$ 0·08; max. iodine-binding power, 0·13%; amylose, 0·7%). The thymol–amylose complex was directly dispersed in boiling water (200 ml.; under nitrogen), and the amylose reprecipitated by saturating the solution with butanol of analytical quality (20 ml.; redistilled over sodium hydroxide), stirring at 95° for ½ hr., and then allowing the solution to cool slowly to room temperature (in a Dewar flask, 24 hr.). The resultant butanol complex was removed on the supercentrifuge, and then redispersed and reprecipitated with butanol. After four butanol re-fractionations the amylose obtained (II*a*) was stored as its butanol complex (*ca.* 240 mg.; O.D.$^{6800}_{4\text{ cm.}}$ 1·21; max. iodine-binding power, 18·7%). 250 mg. of material were obtained when the clear supernatant liquors from each reprecipitation were freeze-dried. Total recovery was approximately 90%, losses being purely mechanical.

To check the value of the limiting iodine-binding power of the amylose, the whole of the above fractionation procedure was repeated with 800 ml. of water to disperse the starch (*ca.* 1·5 g.), and re-fractionation from 400 ml. of water saturated with butanol. Analyses of the fractionation products are given in Table 1. Amylose II*b* was isolated by stirring the butanol complex several times with butanol and then drying it *in vacuo* at 75° (Schoch, *loc. cit.*).

The amylopectin fractions were used without further purification.

Examination of the amylopectin.

Determination of Non-reducing End-group by Periodate Oxidation.—The method described above was used. 0·048 mole of formic acid liberated from 162 g. of amylopectin corresponded to one non-reducing terminal end-group per 23 glucose residues.

Determination of Glucose Residues linked through $C_{(1)}$, $C_{(4)}$, *and* $C_{(6)}$.—0·75% of glucose isolated as above from the periodate-oxidized amylopectin indicated that 82% of the interchain linkages were of the 1 : 6-type.

Methylation of the Amylopectin.—The modification by Hodge, Karjala, and Hilbert (*loc. cit.*) of the liquid-ammonia method of Freudenberg, Boppel, and Meyer-Delius (*Naturwiss.*, 1938, **26**, 123) was used. Dry liquid ammonia, and a reaction temperature of −30°, were essential. After every four additions of reagents the product was isolated, dialysed, and freeze-dried before continuing the treatment. The sample (3 g.) was treated with seventeen additions of reagents, after which the methylated product (2·7 g.) was isolated (Found: OMe, 43·5%), having $[\alpha]_D^{16}$ +204° (*c*, 0·5 in $CHCl_3$). Further methylation was carried out by Purdie and Irvine's method (*J.*, 1903, 1021). The product (2·1 g.) was purified by precipitation from chloroform solution with light petroleum (b. p. 40—60°) (Found: OMe, 43·8. Calc. for tri-*O*-methylamylopectin: OMe, 45·6%).

Hydrolysis of Methylated Amylopectin.—(*a*) The sample (50 mg.) was hydrolysed in a sealed tube by the method of Hough, Hirst, and Jones (*J.*, 1949, 928). The hydrolysate was examined by paper-strip chromatography with butanol–ethanol–water (4 : 1 : 5, v/v) as the mobile phase, and revealed 2 : 3 : 4 : 6-tetra-*O*-methyl- (R_G 1·0 (4·8%), 2 : 3 : 6-tri-*O*-methyl- (R_G, 0·83) (85·0%), di-*O*-methyl- (R_G, 0·59, 0·51) (9·5%), and a trace of mono-*O*-methyl-glucose and glucose. This result indicated the presence of one non-reducing terminal group per 22 ± 1 glucose residues.

(*b*) The material (1·8 g.) was heated with methanolic hydrogen chloride (110 ml.; 1%) for 5 hr. at 100°, then neutralized with silver carbonate, washed, freed from excess of silver with hydrogen sulphide, and concentrated. The syrupy glycosides obtained were boiled with 2% hydrochloric acid (88 ml.) for 8 hr. The solution was then neutralized with silver carbonate as above, deionized by shaking it with resins, and concentrated to give a clear syrup

(1·75 g., 95%). This mixture of methylated glucoses was separated on a column (64 × 3 cm.) of cellulose (Hough, Jones, and Wadman, *J.*, 1949, 2511; Chanda, Hirst, Jones, and Percival, *J.*, 1950, 1289). Elution with butanol–light petroleum (b. p. 100—120°) (3 : 7, v/v) saturated with water gave fractions (1) 0·242 g., (2) 1·172 g., and (3) 0·139 g. By elution with butanol a further fraction (4) 0·058 g. was obtained, whilst elution with water gave a trace of a fraction, which from examination on a paper chromatogram, was mono-*O*-methylglucose and glucose. The last fraction was not examined further.

Examination of the fractions. Fraction (1). Examination by paper-strip chromatography indicated the presence of a single sugar (R_G, 1·0) corresponding to 2 : 3 : 4 : 6-tetra-*O*-methylglucose. Hydrolysis of a small portion (10 mg.) with 2% sulphuric acid, and re-examination revealed an additional substance (R_G, 0·84). Hypoiodite oxidation indicated that fraction (1) contained only 30% of tetra-*O*-methylglucose. Fraction (1) (210 mg.) was then rehydrolysed at 100° with 1% hydrochloric acid (20 ml.) for 5 hr., and the methylated glucoses were separated on Whatman 3MM papers with benzene–ethanol–water (149 : 45 : 15, v/v) as the mobile phase for 4 hr. Elution gave fractions (1*a*) (59 mg.) and (1*b*) (197 mg.) (94% recovery). Hypoiodite oxidation indicated that fraction (1*a*) contained 99% of tetra-*O*-methylglucose. After being recrystallized twice from light petroleum (b. p. 40—60°), the material (50 mg.) had m. p. 85—87°, which was not depressed on admixture with an authentic specimen of tetra-*O*-methyl-D-glucopyranose; $[\alpha]_D^{16}$ +85° (final) (*c*, 0·4 in H_2O) (Found : OMe, 52·0. Calc. for $C_{10}H_{20}O_6$: OMe, 50·5%). The anilide had m. p. 136—138°, alone or mixed with authentic tetra-*O*-methyl-D-glucopyranosylaniline (Found : N, 4·3; OMe, 39·5. Calc. for $C_{16}H_{25}O_5N$: N, 4·5; OMe, 39·9%). From the above results the amount of 2 : 3 : 4 : 6-tetra-*O*-methylglucose was calculated to be 72·3 mg., corresponding to one non-reducing terminal group per 23 glucose residues.

Fraction (1*b*) was shown to consist of a single substance (R_G 0·84) corresponding to 2 : 3 : 6-tri-*O*-methylglucose. It was crystallized from ether and had m. p. 115—117° (alone or mixed with an authentic specimen of 2 : 3 : 6-tri-*O*-methylglucose), $[\alpha]_D^{17}$ +70° (*c*, 0·4 in H_2O), $[\alpha]_D^{17}$ +65° (initial), −35° (final) [*c*, 0·4 in cold methanolic hydrogen chloride (2% for 10 hr.)] (Found : OMe, 41·3. Calc. for $C_9H_{18}O_6$: OMe, 41·9%).

Fraction (2). Paper chromatography indicated that this fraction consisted of one component (R_G 0·84), corresponding to 2 : 3 : 6-tri-*O*-methylglucose. It had m. p. 115—117° (alone or mixed with authentic 2 : 3 : 6-tri-*O*-methyl-D-glucose), $[\alpha]_D^{17}$ +68° (*c*, 1·0 in H_2O), $[\alpha]_D^{17}$ +67° (initial), −36° (final) [*c*, 1·0 in cold methanolic hydrogen chloride (2%, for 10 hr.)] (Found : OMe, 41·5. Calc. for $C_9H_{18}O_6$: OMe, 41·9%).

Fraction (3). Chromatographic examination of this fraction revealed the presence of two substances; one (R_G 0·84) corresponding to 2 : 3 : 6-tri-*O*-methylglucose, the other (R_G 0·59) to 2 : 3-di-*O*-methylglucose. When separated on Whatman 3MM papers and extracted with acetone, a portion gave fractions (3*a*) (18·8 mg.) and (3*b*) (75 mg.) (94% recovery). Fraction (3*a*) was shown to be 2 : 3 : 6-tri-*O*-methylglucose as above. Fraction (3*b*) was chromatographically pure and was a pale yellow syrup, which did not crystallize after two weeks in the cold. It had $[\alpha]_D^{17}$ +106° (initial), +68° (final) (*c*, 1·0 in H_2O) (Found : OMe, 29·3. Calc. for $C_8H_{16}O_6$: OMe, 29·7%). The di-*O*-methylglucose was converted into the gluconolactone and then into 2 : 3-di-*O*-methylgluconophenylhydrazide (Evans, Levi, Hawkins, and Hibbert, *Canad. J. Res.*, 1942, **20**, *B*, 175). The product had m. p. 160—162° (Evans *et al.* give 166·5—167°) (Found : OMe, 19·4; N, 9·0. Calc. for $C_{14}H_{22}O_6N_2$: OMe, 19·7; N, 8·9%).

Fraction (4) was shown chromatographically to consist of 2 : 6- or 3 : 6-di-*O*-methylglucose, or a mixture of the two (R_G 0·51). When it was rehydrolysed and re-examined no other sugar was detected. The fraction was a yellow syrup, which failed to crystallize during two weeks in the cold and had $[\alpha]_D^{17}$ +78° (initial), +60° (final) (*c*, 0·5 in H_2O), $[\alpha]_D^{17}$ +60° (initial), −10° (final) [*c*, 0·5 in methanolic hydrogen chloride (2%; 10 hr. const.)] (Found : OMe, 29·2. Calc. for $C_8H_{16}O_6$: OMe, 29·7%). The uptake of periodate (Bell's method, *J.*, 1948, 992) indicated that 64% of the fraction was 2 : 6-di-*O*-methyl-D-glucose. When excess of periodate was destroyed, the solution evaporated to dryness, and the chloroform-soluble material examined chromatographically, 34% of 3 : 6-di-*O*-methylglucose was found.

Acetylation of the Amylopectin.—Amylopectin (245 mg.) was acetylated with formamide as a dispersive agent (Potter and Hassid, *loc. cit.*). Purification by precipitation from chloroform with light petroleum (b. p. 80—100°) gave a fibrous product (Ap 1) (370 mg., 92%) (Found : Ac, 44·2. Calc. for amylopectin tri-*O*-acetate : Ac, 44·8%), [η] 2·33 (in $CHCl_3$).

Examination of the amylose.

Degradative Effect of Acetylation.—Portions of amylose 1 were acetylated by Higginbotham and Morrison's method (*loc. cit.*) at (*a*) room temperature (16°) for 74 and 186 hr. to yield acetates (A 1) and (A 2) and (*b*) 100° for 4 and 8 hr. to yield acetates (A 3) and (A 4) respectively. The products were purified as above. Acetate A 1 (54 mg.) (Found: Ac, 44·3. Calc. for amylose tri-*O*-acetate: Ac, 44·8%) had $[\eta]$ 2·63 in $CHCl_3$. Acetate A 2 (52 mg.) (Found: Ac, 43·9%) had $[\eta]$ 2·45. Acetate A 3 (47 mg.) (Found: Ac, 44·1%) had $[\eta]$ 2·55. Acetate A 4 (42 mg.) (Found: Ac, 44·0%) had $[\eta]$ 2·38. When the limiting viscosity numbers $[\eta]$ were plotted against the time of reaction (t), the rate of breakdown was so small that it was assumed legitimate to extrapolate the $[\eta]$–t curve to zero time to obtain the limiting viscosity number of the undegraded amylose. This enabled the rate of degradation to be calculated and showed that minimum degradation occurred at room temperature in the time required to give complete acetylation.

Molecular weights (M) and corresponding degrees of polymerization (D.P.) were later calculated from the equation $M = 1{\cdot}3 \times 10^5 \times [\eta]$ (where $[\eta]$ is the limiting viscosity number) obtained from the osmotic pressure measurements, as shown in Table 3.

TABLE 3. *Results of viscosity measurements.*

Product	Acetylation time (hr.)	$[\eta]$	$10^{-5}M$	Approx. D.P.	Rate of degradation *
A 1	74	2·63	3·42	1190	0·001
A 2	146	2·45	3·19	1110	0·001
A 3	4	2·55	3·32	1150	0·025
A 4	8	2·38	3·10	1080	0·023
—	0	2·80 †	3·64 †	1260 †	—

* Expressed as the number of bonds broken per initial amylose molecule per hr.
† Extrapolated values.

Acetylation of Amylose 2a.—Amylose–butanol complex (containing *ca.* 240 mg. of amylose) was acetylated as above for three days at room temperature, to yield amylose acetate (A 5) (400 mg.) (Found: OAc, 44·3%), $[\eta]$ 3·35.

Physical measurements.

Measurements of Limiting Viscosity Number.—The limiting viscosity number $[\eta]$ for the acetylated products was determined from the relation $[\eta] = \lim_{c \to 0} (\eta_{sp.}/c)$. Specific viscosities ($\eta_{sp.}$) in chloroform solution were determined with a modified Ubbelohde viscometer (Davis and Elliott, *J. Coll. Sci.*, 1949, **4**, 313) at 22·5° ± 0·001°. Solvent flow time was 192·0 sec. By measuring the viscosity of a series of liquids, the kinetic-energy correction factor B in the equation $\eta = Adt + Bd/t$ (d = density of liquid) for a capillary viscometer was shown to be zero. The viscosity of the most concentrated solution was measured first, and the dilutions were made *in situ* in the viscometer. Final concentrations (c) were determined in duplicate by the method described by Gilbert, Graff-Baker, and Greenwood (*J. Polymer Sci.*, 1951, **6**, 585) and were expressed as g. per 100 ml. of solution. Results were as tabulated.

Product	c	$\eta_{sp.}$	$\eta_{sp.}/c$	Product	c	$\eta_{sp.}$	$\eta_{sp.}/c$
A 1	0·201	0·705	3·51	A 2	0·210	0·626	2·98
	0·134	0·436	3·25		0·140	0·399	2·85
	0·100	0·307	3·06		0·105	0·286	2·73
	0	—	2·63 *		0	—	2·45 *
A 3	0·186	0·568	3·05	A 4	0·200	0·536	2·85
	0·124	0·375	3·02		0·133	0·336	2·68
	0·093	0·274	2·95		0·100	0·258	2·58
	0	—	2·55 *		0	—	2·38 *
A 5	0·575	2·376	4·13	Ap 1	0·540	1·568	2·90
	0·384	1·533	3·99		0·360	0·956	2·68
	0·287	1·102	3·84		0·270	0·675	2·50
	0·230	0·839	3·65		0·216	0·547	2·53
	0·192	0·687	3·58		0·180	0·443	2·46
	0·143	0·522	3·65		0·135	0·340	2·52
	0·115	0·463	3·53		0·108	0·263	2·40
	0	—	3·35 *		0	—	2·33 *

* Extrapolated values.

Measurements were also carried out on the unsubstituted components dissolved in M-potassium hydroxide. The viscometer used had a solvent flow time of 227 sec., and no kinetic-energy correction was necessary. Solutions were prepared by shaking polysaccharide (50—100 mg.) in M-potassium hydroxide (15 ml.) vigorously at room temperature for 30 min. Before being placed in the viscometer, each solution was filtered under gravity through sintered glass (G3, then G4). The results, which were reproducible in the short time required for dissolution and measurement, are tabulated. Measurements on a sample of rabbit-liver glycogen in the same solvent are also included.

Product	c	$\eta_{sp.}$	$\eta_{sp.}/c$	Product	c	$\eta_{sp.}$	$\eta_{sp.}/c$
Amylose	0·333	0·960	2·88	Amylopectin ...	0·474	0·766	1·62
	0·222	0·585	2·64		0·316	0·443	1·41
	0·167	0·417	2·50		0·237	0·313	1·32
	0·111	0·265	2·39		0·158	0·193	1·22
	0	—	2·15 *		0	—	1·02 *
Glycogen	0·666	0·073	0·110				
	0·333	0·035	0·105				
	0·267	0·029	0·108				
	0·167	0·017	0·102				
	0	—	0·100 *				

* Extrapolated values.

Measurement of Osmotic Pressure (with W. N. Broatch).—Osmotic pressures (π) of amylose acetate (A5) in chloroform were determined at 22·5°. The osmometer used was a modified Fuoss–Mead instrument (*J. Phys. Chem.*, 1943, **47**, 59) designed for complete immersion in a thermostat (cf. Masson and Melville, *J. Polymer Sci.*, 1949, **4**, 323). The membrane was of gel-cellophane (No. 600) conditioned to solvent after dehydration with acetone–water mixtures. It was held taut in the osmometer by rings (cf. Gilbert, Graff-Baker, and Greenwood, *loc. cit.*). Observed osmotic pressures (measured to 0·001 cm.) were corrected for the solution density (*idem*, *loc. cit.*). Density determinations showed that this correction was $-0{\cdot}002\ h_s c$ (h_s = height from the mid-point of the vertical membrane to the solution meniscus; c = concentration), and the results shown in Fig. 2 include this. Concentrations were estimated in duplicate as above.

Measurements on amylopectin acetate (Ap 1) were made in the osmometer previously described (*idem*, *loc. cit.*), in which for greater ease in manipulation, the solvent capillary diameter was altered to 0·04 cm. The membrane was as above. The density correction was $+0{\cdot}003\ h_s c$, and is included in the results shown in Fig. 2.

In each experiment, the value of the intercept $(\pi/c)_0$ was obtained from the graph of π/c *versus* c and was found to be 0·380 and 0·097 for amylose acetate and amylopectin acetate, respectively. Substitution of these values in van't Hoff's equation gave the number-average molecular weights ($\bar{M}_n$), since $\bar{M}_n = \boldsymbol{R}T(c/\pi)_0/100d_0\boldsymbol{g}$ ($\boldsymbol{R}$ = $8{\cdot}315 \times 10^7$ ergs/degree/mole; $\boldsymbol{g}$ = gravitational constant; and d_0 = density of chloroform at 22·5°). The value of $\bar{M}_n$ was $4{\cdot}4 \times 10^5$ for A 5 and $1{\cdot}8 \times 10^6$ for Ap 1.

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The Reactions of Highly Fluorinated Organic Compounds. Part VI. Octafluorocyclohexa-1 : 3- and -1 : 4-diene and Difluoromalonic Acid.*

By D. E. M. Evans and J. C. Tatlow.

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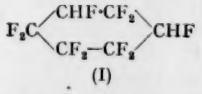
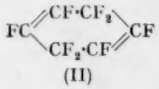
Dehydrofluorination of 1*H* : 3*H*-decafluoro*cyclo*hexane † affords both octafluoro*cyclo*hexa-1 : 3- and -1 : 4-diene. The former is oxidised to tetrafluorosuccinic acid, and the latter to difluoromalonic acid which is a comparatively stable acid.

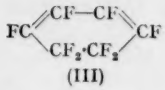
In a recent communication (Barbour, Mackenzie, Stacey, and Tatlow, *J. Appl. Chem.*, 1954, **4**, 347) the fluorination of benzene, with cobaltic fluoride at 150°, was described. Among the products was a decafluoro*cyclo*hexane (b. p. 78°) which was identified tentatively as having a 1*H* : 3*H*-structure (I). We now report further investigations on the exhaustive dehydrofluorination of this compound. Refluxing with concentrated aqueous potassium hydroxide eliminated 2 mols. of hydrogen fluoride and gave material of molecular formula C_6F_8, separated by fractional distillation into two octafluoro*cyclo*hexadienes. One of these (b. p. 57—58°) was the 1 : 4-diene (II), since with permanganate it gave difluoromalonic acid, identified as the free acid, organic salts, and the diamide. Addition of bromine to



(I)



(II)



(III)

the 1 : 4-diene (II) gave, first, 4 : 5-dibromo-octafluoro*cyclo*hex-1-ene, and then 1 : 2 : 4 : 5-tetrabromo-octafluoro*cyclo*hexane. The diene and its dibromide both gave characteristic infra-red C=C bands, the intensity of that from the former being about twice those of analogous mono-olefins (including the latter). The 1 : 4-diene (II) appears to be the same compound as that obtained by McBee, Lindgren, and Ligett (*Ind. Eng. Chem.*, 1947, **39**, 378; U.S.P. 2,432,997, 2,586,364; *Chem. Abs.*, 1948, **42**, 2618; 1952, **46**, 8675) by fluorination of hexachlorobenzene (using BrF_3 and then SbF_5), followed by dehalogenation. These authors, however, did not work out its structure.

The second diolefin from the original dehydrofluorination reaction had b. p. 63—64° and was rather unstable (see p. 3780). It was shown to be octafluoro*cyclo*hexa-1 : 3-diene (III) as follows. Permanganate oxidation afforded tetrafluorosuccinic acid, identified as two well-characterised derivatives. Bromine addition gave a dibromo-octafluoro*cyclo*hexene fraction, probably a mixture, and then 1 : 2 : 3 : 4-tetrabromo-octafluoro*cyclo*hexane, and addition of chlorine gave the analogous 1 : 2 : 3 : 4-tetrachloro-compound. In infra-red spectroscopic measurements, the conjugated diene (III) showed two distinct C=C bands, the sum of their intensities being approximately equal to the intensity of the one band given by the 1 : 4-diene (II). The dibromo-addition product of (III) gave a broad C=C band, of lower intensity; this may have been due to the presence of isomers.

All these observations confirm that the decafluoro*cyclo*hexane (b. p. 78°) is in fact a 1*H* : 3*H* compound (I), if it is assumed that migration of fluorine cannot occur in the types of reaction used. The earlier work (Barbour *et al.*, *loc. cit.*) showed that the compound could not have a 1*H* : 4*H*-structure, whilst the isolation of the two dienes (II) and (III) rules out the possibility that it might be a 1*H* : 2*H*-compound. It seems that in a 1*H* : 3*H*-compound (I) fluorine can be removed from either of the $\cdot CF_2\cdot$ groups flanking a CHF group. The mode of elimination from the isomeric 1*H* : 2*H*-type of structure is described by Roylance, Tatlow, and Worthington (*J.*, in the press).

There seems to be only one previous reference to difluoromalonic acid. Henne and DeWitt (*J. Amer. Chem. Soc.*, 1948, **70**, 1548) oxidised 3 : 3-difluoropenta-1 : 4-diene and

* Part V, *J.*, 1954, 1177.

† For this use of *H*, see *Chem. Eng. News*, 1952, **30**, 4515, and *J.*, 1952, 5059.

3 : 3-difluorohexachloropenta-1 : 4-diene with alkaline permanganate. They did not purify the acid but obtained the dimethyl ester and the diamide. The melting points of their amide and of ours agree well. Henne and DeWitt implied that free difluoromalonic acid was decarboxylated readily even in the cold. However, the acid isolated in the present work, though very deliquescent, was quite stable under normal conditions. It was best purified by distillation *in vacuo* and was recovered after being heated at 200°. After 20 hr. at 10—15° with 2N-sodium hydroxide negligible amounts of fluorine had been removed, and only 10% or so was hydrolysed after 3 hr. at 100° with 5N-alkali. Though perhaps rather less stable than the higher members of the homologous perfluorodicarboxylic acid series, difluoromalonic acid appears to be similar to them in many respects.

Experimental

Dehydrofluorination of 1H : 3H-*Decafluoro*cyclo*hexane*.—The decafluoro-compound (120 g.; b. p. 78°, m. p. 39°; Barbour *et al.*, *loc. cit.*) was boiled for 6 hr. with potassium hydroxide (200 g.) in water (200 c.c.). The organic phase was separated, washed with water, dried ($MgSO_4$), and fractionated through a 2′ column. The fractions obtained, all colourless mobile liquids, were: (i) octafluoro*cyclo*hexa-1 : 4-diene (25·6 g.), b. p. 57—58°, n_D^{18} 1·318 (Found: C, 32·3; F, 67·4. Calc. for C_6F_8: C, 32·2; F, 67·8%); (ii) mixed dienes (17·5 g.), b. p. 58—63°; (iii), *octafluoro*cyclo*hexa*-1 : 3-*diene* (14·4 g.), b. p. 63—64°, n_D^{18} 1·329 (Found: C, 31·9; F, 68·0%); and (iv) residue (16·0 g.), b. p. above 64°. McBee, Lindgren, and Ligett (*loc. cit.*) gave b. p. 56—57°, n_D^{20} 1·3148, for perfluoro*cyclo*hexadiene.

The 1 : 3-diene is apparently unstable and decomposed slowly at room temperature. After 1—2 days the sample was turbid, hydrogen fluoride appeared to be present, and analysis gave carbon figures 1—2% low with a little hydrogen (*ca.* 0·5%) then appearing as well.

Infra-red spectroscopic examination of the 1 : 4-diene showed the presence of a C=C band at 1739 cm.$^{-1}$ of which the intensity was about twice that of the bands, also at 1739 cm.$^{-1}$, given by decafluoro*cyclo*hexene, or the nonafluoro*cyclo*hexene obtained from the 1*H* : 3*H*-decafluoro-compound (Barbour *et al.*, *loc. cit.*). The 1 : 3-diene showed two bands, at 1713 and 1753 cm.$^{-1}$, with a total optical density approximately equal to that of the one band given by the 1 : 4-diene. The measurements were made on carbon tetrachloride solutions (0·1—0·2M) with a Grubb-Parsons spectrometer with a rock-salt prism.

The 1 : 3-diene gave a band in the ultra-violet at (max.) λ 2560 Å, ε approx. 3160 (*c* 0·10 g./l. in diethyl ether). The 1 : 4-diene showed no selective absorption in this region. No great accuracy is claimed for these figures because of the instability of the diene and the volatility of the solution.

Addition of Bromine to the 1 : 4-*Diene*.—(*a*) The olefin (4·0 g.; b. p. 57°) and bromine (12·0 g.), in a hard-glass flask, were irradiated with ultra-violet light for 17 hr., the heat from the lamp causing gentle reflux. After being washed with aqueous sodium pyrosulphite and dried (P_2O_5), the organic phase was distilled, to give 4 : 5-*dibromo-octafluoro*cyclo*hex*-1-*ene* (3·5 g.), b. p. 40°/13 mm., 50°/20 mm. (Found: C, 19·0; F, 39·5. $C_6Br_2F_8$ requires C, 18·8; F, 39·6%), and 1 : 2 : 4 : 5-*tetrabromo-octafluoro*cyclo*hexane* (0·5 g.), b. p. 99°/20 mm., m. p. 40—42° (Found: C, 13·0; F, 28·0. $C_6Br_4F_8$ requires C, 13·25; F, 28·0%). 4 : 5-Dibromo-octafluoro*cyclo*hex-1-ene gave a C=C band in the infra-red at 1754 cm.$^{-1}$.

(*b*) When the experiment was carried out for 48 hr., the dibromide (1·0 g.) and the tetrabromide (3·1 g.) were obtained. Re-treatment of the dibromide and intermediate fractions (1·6 g.) for 24 hr. gave the tetrabromide (1·2 g.), m. p. 42°.

Additions of Bromine and Chlorine to the 1 : 3-*Diene*.—(*a*) The olefin (1·70 g.; b. p. 63°) and bromine (2·7 g.) were treated as in the case of the isomeric diene to give dibromo-octafluoro-*cyclo*hexenes (1·00 g.), b. p. 54—56°/20 mm., 74°/100 mm. (Found: C, 19·0; F, 39·7%), and 1 : 2 : 3 : 4-*tetrabromo-octafluoro*cyclo*hexane* (1·10 g.), b. p. 105°/20 mm., m. p. 42—43° (Found: C, 13·3; F, 28·1%).

(*b*) The olefin (2·3 g.) and chlorine (4·0 g.) were sealed in a hard-glass tube which was irradiated with ultra-violet light for 24 hr. Isolation as usual afforded 1 : 2 : 3 : 4-*tetrachloro-octafluoro*cyclo*hexane* (2·80 g.), b. p. 49—50°/20 mm., m. p. 59—60° (Found: C, 19·9; F, 41·2. $C_6Cl_4F_8$ requires C, 19·7; F, 41·5%).

Difluoromalonic Acid.—Octafluoro*cyclo*hexa-1 : 4-diene (10·0 g.), potassium permanganate (60 g.), and water (60 c.c.) were shaken together for 17 hr. at 95° in a rocking autoclave. The

acidic product, after isolation and extraction as described in earlier papers, was heated at 100°/15 mm. for 5 min. and then taken up in dry ether, the small inorganic impurity filtered off, and the solvent evaporated. The residue, after being dried *in vacuo* as before, was a deliquescent acidic solid (8·4 g.), m. p. 115°. By distillation of this solid (1 g.) at 135° (bath-temp.)/15 mm. on to a cold finger, there was obtained *difluoromalonic acid* (0·9 g.), m. p. 117—118° (Found: C, 25·8; H, 1·6%; equiv. 69·6. $C_3H_2O_4F_2$ requires C, 25·7; H, 1·4%; equiv. 70·0). No fluoride ion was detected in the titration liquors.

The acid may be recrystallised from dry benzene but the above method of purification is preferable.

To the crude acid (1·00 g.) in ether (5 c.c.), aniline was added dropwise until precipitation was complete. The solid was filtered off and recrystallised twice from acetone–chloroform, to give the *dianilinium* salt (1·50 g.), m. p. 160—161° (Found: C, 55·5; H, 4·9; F, 11·5%; equiv. 165. $C_{15}H_{16}O_4N_2F_2$ requires C, 55·2; H, 4·9; F, 11·6%; equiv., 163).

The crude acid (0·30 g.) was dissolved in aqueous sodium hydroxide, the pH adjusted to *ca.* 4 with hydrochloric acid, and aqueous *S*-benzylthiuronium chloride added. The precipitate was recrystallised from water to give *di*-(S-*benzylthiuronium*) *difluoromalonate* (0·80 g.), m. p. 180—182° (Found: C, 48·3; H, 4·8. $C_{19}H_{22}O_4N_4S_2F_2$ requires C, 48·3; H, 4·7%).

Fluorosulphonic acid (0·5 c.c.) was added to the crude acid (1·00 g.) in ethyl alcohol (8·0 c.c.). After the initial vigorous reaction, the mixture was refluxed for 15 min. Water was added, the residual oil was extracted with ether, the extracts were dried ($MgSO_4$) and filtered, and ammonia gas was passed through. After 17 hr. at 10—15°, the solvent was evaporated and the residue was recrystallised from water to give difluoromalondiamide (0·64 g.), m. p. 206—207° (Found: C, 25·9; H, 2·8; F, 27·5. Calc. for $C_3H_4O_2N_2F_2$: C, 26·1; H, 2·9; F, 27·5%). Henne and DeWitt (*loc. cit.*) cited m. p. 206·4° ± 0·2°.

When pure difluoromalonic acid was heated to 200° for 20 min., no evolution of carbon dioxide was detected. The recovered acid had m. p. 115—116° and gave a dianilinium salt, m. p. 160—161°.

The pure acid was heated for 3 hr. at 100° with 5N-sodium hydroxide. Determination of the fluoride ion content of the solution showed that about 10% of that present in the original acid had been removed. After treatment of the aqueous solution by acidification, extraction, etc., as before, only difluoromalonic acid (80% recovery), m. p. 112—114°, was obtained. This gave the dianilinium salt, m. p. 160—161° (Found: equiv., 164). When the acid was kept for 20 hr. at 10—15° in 2N-sodium hydroxide, less than 1% of the fluorine was removed as ionic fluoride.

Tetrafluorosuccinic Acid Derivatives.—Octafluoro*cyclo*hexa-1 : 3-diene (5·5 g.) was oxidised with potassium permanganate (40 g.) in water (60 c.c.), in a rocking autoclave at 100° for 24 hr. After isolation as previously described (Buxton and Tatlow, *J.*, 1954, 1177) there was obtained crude tetrafluorosuccinic acid (3·8 g.), m. p. 115—116°, which was converted into the dianilinium salt (60% based on acid), m. p. 224—225° (Found: C, 51·1; H, 4·3; F, 19·7%; equiv., 189. Calc. for $C_{16}H_{16}O_4N_2F_4$: C, 51·1; H, 4·3; F, 20·2%; equiv., 188), and into the diamide (67% based on acid), m. p. 258—259° (Found: C, 25·7; H, 2·1; F, 40·0. Calc. for $C_4H_4O_2N_2F_4$: C, 25·5; H, 2·1; F, 40·4%). Reported values (*idem, loc. cit.*) are m. p. 224—225° (salt) and m. p. 259° (amide).

The acid gave a *di*-(S-*benzylthiuronium*) salt (60%; from water), m. p. 189—190° (Found: C, 46·3; H, 4·0. $C_{20}H_{22}O_4N_4S_2F_4$ requires C, 46·0; H, 4·2%).

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8-*Hydroxyquinaldic Acid.*

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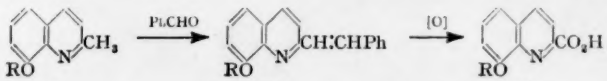
8-Hydroxyquinaldic acid, a potential chelating agent, is obtainable by demethylation of 8-methoxyquinaldic acid prepared from 8-methoxyquinaldine by treatment with selenium dioxide or more conveniently by oxidation of its 2-styryl derivative.

During an investigation of the structure of xanthurenic acid, Musajo and Minchilli (*Ber.*, 1941, **74**, 1839) obtained a few milligrams of 8-hydroxyquinaldic acid (III; R = H) by the catalytic dehalogenation of the 4-chloro-8-hydroxy-acid. The preparation of this substance on a larger scale was undertaken since it combines the functional groups of 8-hydroxyquinoline ("oxine") and quinaldic acid, two analytical reagents widely used for metals, and as a potentially tridentate chelating agent its reactions with cations of different radii and charges should be of interest.

The oxidation of the methyl group of 8-hydroxyquinaldine (I; R = H) could not be effected without destruction of the benzenoid ring. The phenolic hydroxyl group was therefore protected by methylation, but treatment of 8-methoxyquinaldine (I; R = Me) with selenium dioxide gave only a poor yield of 8-methoxyquinaldic acid (III; R = Me), the main product being an intractable red viscous material from which small amounts of 8-methoxyquinoline-2-aldehyde could be obtained with difficulty.



(I) (II) (III)

By heating 8-methoxyquinaldine (I; R = Me) with anhydrous zinc chloride and excess of benzaldehyde at 150—160° for 10 hr. Tröger and Dunker (*J. pr. Chem.*, 1925, **109**, 88) obtained what they described as 8-methoxy-2-styrylquinoline (II; R = Me), as "a dirty yellow amorphous product"; only the hydrochloride could be purified or analysed. In our hands this method invariably gave an amorphous yellow-green solid, m. p. >360°, which did not decolorise cold permanganate solution or bromine water and was unattacked in acetic acid solution by ozone or by 30% hydrogen peroxide: qualitative tests established the presence of zinc. When, however, 8-methoxyquinaldine in acetic anhydride was condensed with a three-fold excess of benzaldehyde, the zinc chloride being omitted, an excellent yield of authentic 8-methoxy-2-styrylquinoline (II; R = Me) resulted. After purification through the hydrochloride it formed creamy-white crystals, m. p. 100°, with properties agreeing in the main with those of the product which Tröger and Dunker prepared by condensing 8-methoxyquinaldine and benzaldehyde in the absence of zinc chloride and for which they reported analytical results suggesting that it was 2-(2-hydroxy-2-phenylethyl)-8-methoxyquinoline. In pyridine solution the styryl compound (II; R = Me) was oxidised almost quantitatively by cold permanganate solution to 8-methoxyquinaldic acid (III; R = Me). Demethylation proved difficult, in agreement with previous observations with similar derivatives of 8-methoxyquinoline (cf. Phillips, Elbinger, and Merritt, *J. Amer. Chem. Soc.*, 1949, **71**, 3986) but refluxing the 8-methoxy-acid with potassium iodide and 95% phosphoric acid (cf. Furst and Olsen, *J. Org. Chem.*, 1951, **16**, 412) gave 8-hydroxyquinaldic acid (III; R = H) in almost theoretical yield. The m. p. (211°) of the compound after recrystallisation from aqueous dioxan was depressed by recrystallisation from aqueous alcohol, probably in consequence of unusually ready ester formation: we have noted similar behaviour with 4-chloro(or 4-bromo)-8-hydroxyquinaldic acid.

The condensation of aromatic aldehydes with heterocyclic compounds possessing a reactive methyl group may yield side-chain alcohols or styryl compounds according to

conditions, the presence of acetic anhydride or zinc chloride favouring the latter (cf. Tröger and Dunker, *loc. cit.*; Royer, *J.*, 1949, 1803), while in the absence of zinc chloride the secondary alcohol is often stated to be the sole product. Phillips, Elbinger, and Merritt (*loc. cit.*) condensed 8-hydroxyquinaldine (I; R = H) with benzaldehyde in the absence of zinc chloride and obtained a product, m. p. 104—105° after vacuum distillation, which they formulated as 8-hydroxy-2-styrylquinoline (II; R = H) although the analytical figure (Found: N, 5·47%) lay between the values for the styryl compound (5·67%) and the alcohol (5·28%) and no chemical evidence of side-chain unsaturation was advanced. However, the hydrolysis with alcoholic sodium hydroxide or with hydrochloric acid of 8-acetoxy-2-styrylquinoline (II; R = Ac), obtained by condensing 8-hydroxyquinaldine with benzaldehyde in acetic anhydride as solvent, gave authentic 8-hydroxy-2-styrylquinoline, m. p. 103—104°, identical with a specimen made by the procedure described by Phillips *et al.* (*loc. cit.*).

The oxidation of 8-hydroxy-2-styrylquinoline by aqueous permanganate proved difficult to control, and the best yield of 8-hydroxyquinaldic acid (20%) could not be reproduced consistently. The most convenient route to this acid is therefore through the styryl derivative of 8-methoxyquinaldine.

8-Hydroxyquinaldic acid gives a deep green colour with traces of ferric ions. Its coloration and precipitation reactions with other inorganic ions will be reported elsewhere.

Experimental

8-Methoxyquinaldine (I; R = Me).—The preparation of this base has been examined by numerous workers since Doebner and Miller (*Ber.*, 1884, **17**, 1698) obtained it in low yield. *o*-Nitrophenol, picric acid, and arsenic pentoxide have been recommended as oxidising agents but Phillips, Elbinger, and Merritt (*loc. cit.*) found that there is no effective oxidising agent specially to be preferred when αβ-unsaturated compounds are condensed with *o*-anisidine, and omit one in their preparation of 8-methoxyquinoline. Although Spivey and Curd (*J.*, 1949, 2656) found the use of *m*-nitrobenzenesulphonic acid as a water-soluble oxidising agent trebled the yield of 5- and 7-chloroquinaldines in the Doebner–Miller synthesis, it showed no special value in the present preparation. If, however, the reactants are preheated before addition of oxidising agent, and the duration of heating and the proportion of *o*-nitrophenol are limited to the values given below, the tedious steam-distillation of excess of oxidant can be avoided, while the formation of tar is reduced and the overall yield improved.

Crotonaldehyde (40 g., 1·14 mol.) was added during 15 min. to a solution of *o*-anisidine (61·5 g., 1 mol.) and *o*-nitrophenol (7·0 g., 0·1 mol.) in 10N-hydrochloric acid (100 ml.) previously heated to 100°. After a further 2 hours' heating the mixture was cooled and very slowly neutralised with concentrated aqueous sodium hydroxide. Next morning the semisolid product was collected, washed thoroughly with water, and dried in air. Distillation at 22—28 mm. gave 8-methoxyquinaldine, b. p. 145—160° which was recrystallised from hot benzene (animal charcoal), giving needles (38—42 g.; 44—49%), m. p. 125°.

8-Methoxy-2-styrylquinaldine (II; R = Me).—8-Methoxyquinaldine (3·0 g.), freshly distilled benzaldehyde (2·76 g.), and acetic anhydride (8·0 g.) were refluxed for 3 hr. at 160°. After being cooled the mixture was poured into water (100 ml.), and cautiously neutralised with sodium hydroxide solution. The viscous solid which then separated was taken up in ether (3 × 100 ml.), and after filtration the solution was saturated with dry hydrogen chloride; *8-methoxy-2-styrylquinoline hydrochloride* then separated and was crystallised from hot 10N-hydrochloric acid, forming bright yellow needles, m. p. 226° (decomp.) (Found: Cl, 11·7. $C_{18}H_{15}ON,HCl$ requires Cl, 11·9%). Neutralisation of a cold aqueous solution of this hydrochloride with dilute sodium hydroxide gave *8-methoxy-2-styrylquinoline* as needles, m. p. 100° (from aqueous alcohol) (Found: C, 82·8; H, 5·9. $C_{18}H_{15}ON$ requires C, 82·8; H, 5·8%). Its properties agreed closely with those of the product described by Tröger and Dunker (*loc. cit.*) as 2-(2-hydroxy-2-phenylethyl)-8-methoxyquinoline. Their preparation of alleged 8-methoxy-2-styrylquinoline by condensation of 8-methoxyquinaldine and benzaldehyde in the presence of zinc chloride, gave, in our hands, even when the experimental conditions were widely varied, only an amorphous substance containing zinc which sintered below 300° but had not melted at 360°. It was completely insoluble in hydrochloric acid, acetic acid, and all common solvents except cold pyridine and boiling nitrobenzene. It was unchanged by boiling dilute acids or alkalis, and by oxidising agents such as ozone, hydrogen peroxide, or potassium permanganate.

8-*Methoxyquinaldic Acid* (III; R = Me).—(a) *By oxidation of* 8-*methoxy*-2-*styrylquinoline*. 8-Methoxy-2-styrylquinoline (6·3 g.) dissolved in pyridine (20 ml.) was cooled in ice-water and shaken continuously while 4% aqueous potassium permanganate was added slowly until the colour just persisted. The precipitate of manganese dioxide was collected and washed well with hot water. The washings and the yellow filtrate were combined, concentrated to 50 ml. on a water-bath, and filtered while hot. On acidification a dense yellow precipitate separated and was collected, pressed dry, and washed with ether (3 × 50 ml.). The residual crude 8-methoxyquinaldic acid (3·9 g.; m. p. 150°) was crystallised from benzene containing a little alcohol; golden-yellow needles of the *monohydrate*, m. p. 158—159°, separated (Found: C, 59·5; H, 5·0; N, 6·2. $C_{11}H_9O_3N,H_2O$ requires C, 59·7; H, 5·0; N, 6·3%).

On recrystallising this monohydrate from hot water, large crystals of the *dihydrate*, m. p. 121—122°, were obtained (Found: C, 55·1; H, 5·2. $C_{11}H_9O_3N,2H_2O$ requires C, 55·2; H, 5·4%). The dihydrate is the form stable in moist air but it may be transformed into the monohydrate at 100° or by recrystallisation from benzene–alcohol. When heated *in vacuo* in a drying pistol the monohydrate slowly loses weight; but this is due rather to sublimation than to loss of water since there is no change in the melting point of the residue.

(b) *From the oxidation of* 8-*methoxyquinaldine with selenium dioxide*. Freshly sublimed, finely powdered selenium dioxide (6·14 g.) was added during 15 min. to a solution of 8-methoxyquinaldine (6·36 g.) in boiling xylene (100 ml.). The theoretical weight of selenium separated almost immediately and was filtered off from the boiling solution. On removing the solvent in a current of air, yellow crystals separated together with a red viscous material. Purification of the yellow crystals gave 8-methoxyquinaldic acid monohydrate (0·6 g.), m. p. 159° (from benzene containing a little alcohol). The red viscous material was extracted with hot benzene, filtered, and the solvent allowed to evaporate slowly in the air. From the pale yellow solid which separated (1·6 g.), accompanied by a considerable amount of red viscous material, fractional crystallisation from aqueous alcohol, followed by vacuum sublimation, and finally a series of recrystallisations from water gave 8-*methoxyquinoline*-2-*aldehyde* as faintly green, long needles, m. p. 102° (Found: C, 70·3; H, 4·4. $C_{11}H_9O_2N$ requires C, 70·6; H, 4·8%). The 2 : 4-*dinitrophenylhydrazone* formed orange plates from 95% alcohol, m. p. 260° (decomp.) (Found: N, 28·0. $C_{17}H_{13}O_5N_5$ requires N, 28·3%).

8-*Hydroxyquinaldic acid* (III; R = H).—A mixture of 8-methoxyquinaldic acid monohydrate (1·3 g.), potassium iodide (3·25 g.), and syrupy phosphoric acid (10·9 g.) was refluxed at 215—225°. A red colour appeared in the condenser, and heating was continued until this vanished (about 2 hr.). When cold the mixture was poured into vigorously stirred water (100 ml.); crude 8-hydroxyquinaldic acid [1·35 g.; m. p. 195° (with sublimation and decomp.)] separated as a yellow solid. This was collected, after being set aside overnight, and freed from accompanying tarry material first by solution in 1% potassium hydroxide and reprecipitation from the filtered solution by hydrochloric acid, then by careful neutralisation of its solution in sodium hydrogen carbonate solution. Finally it was crystallised from aqueous dioxan, forming fine yellow crystals, m. p. 211°, which when powdered readily cohere as a more orange product (Found: C, 63·5; H, 3·8; N, 7·75. $C_{10}H_7O_3N$ requires C, 63·5; H, 3·7; N, 7·4%). To avoid introducing metallic impurities only "AnalaR" reagents and redistilled pure solvents were used in this preparation.

8-Hydroxyquinaldic acid is insoluble in light petroleum, benzene, xylene, or chloroform; it is soluble in hot alcohol, dioxan, amyl alcohol, and glacial acetic acid, and readily soluble in acetone and in dilute solutions of alkalis and mineral acids. A dilute solution of the acid in acetone gave a deep green colour with traces of ferric iron. Attempts to crystallise this acid from aqueous alcohol resulted in lowering of the melting point by 10—20°, the bright yellow colour fading to a pale straw. This behaviour (which has also been observed in these laboratories with 4-bromo-8-hydroxyquinaldic acid) may be due to partial esterification, for the original melting point is recovered by dissolution in aqueous bicarbonate and precipitation with acid.

8-*Acetoxy*-2-*styrylquinoline* (II; R = Ac).—8-Hydroxyquinaldine (5·2 g.), prepared according to Phillips, Emery, and Price (*Analyt. Chem.*, 1952, **24**, 1033), was heated for 3 hr. at 160° with benzaldehyde (5·3 g.) and acetic anhydride (7·0 g.). After cooling, the pale red oil was poured slowly into vigorously stirred water (100 ml.), a yellow solid immediately separating. 5% Sodium hydroxide solution was then added until a slight, permanent alkaline reaction was obtained. The precipitate, which was contaminated with benzaldehyde, was collected and dried. After recrystallisation successively from aqueous alcohol, aqueous dioxan, and light petroleum (b. p. 60—80°), 8-*acetoxy*-2-*styrylquinoline* (4·3 g.) separated as very pale brown

needles, m. p. 119—120°, which were insoluble in 2N-sodium hydroxide (Found: C, 78·6; H, 5·1. $C_{19}H_{15}O_2N$ requires C, 78·9; H, 5·2%).

Hydrolysis. 8-Acetoxy-2-styrylquinoline (5·5 g.) was refluxed for 2 hr. with 5% sodium hydroxide solution (50 ml.). The mixture was neutralised with 5N-hydrochloric acid, and the 8-hydroxy-2-styrylquinoline which then separated was dried and recrystallised from light petroleum and then from aqueous alcohol forming yellow crystals (3·2 g.), m. p. 102—103°, which readily decolorised potassium permanganate solution (Found: C, 82·3; H, 5·5. Calc. for $C_{17}H_{13}ON$: C, 82·6; H, 5·3%). It did not depress the melting point of a sample prepared in 36% yield by Phillips, Elbinger, and Merritt's method (*loc. cit.*) (Found: C, 82·3; H, 5·3%). Oxidation with aqueous potassium permanganate in the cold gave 8-hydroxyquinaldic acid, but in variable yield.

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Action of Alcoholic Potassium Hydroxide on 3 : 4-*Dihydro*-1-2′-*nitrobenzyl*isoquinolines.

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3 : 4-Dihydro-6 : 7-dimethoxy-1-(3-methoxy-2-nitrobenzyl)*iso*quinoline ($C_{19}H_{20}O_5N_2$) in refluxing methanolic potassium hydroxide gave a compound $C_{19}H_{16}O_4N_2$ (A), a compound $C_{19}H_{18}O_5N_2$ (B), and 3 : 4-dihydro-6 : 7-dimethoxy*iso*carbostyril. Structures are suggested for the compounds A and B on the basis of their reactions and light absorptions. Four other 3 : 4-dihydro-1-2′-nitrobenzyl*iso*quinolines were also shown to yield compounds analogous to A, on treatment with methanolic potassium hydroxide, by loss of 4 hydrogen atoms and one oxygen atom.

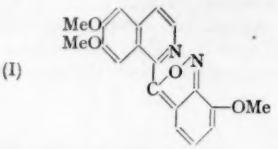
SEVERAL 1-benzyl-3 : 4-dihydro*iso*quinolines have been converted into the corresponding 1-benzoyl*iso*quinolines by treatment with hot methanolic potassium hydroxide (Späth, Reidl, and Kubiczek, *Monatsh.*, 1948, **79**, 72; Noller and Azima, *J. Amer. Chem. Soc.*, 1950, **72**, 17; Julian, Karpel, Magnani, and Meyer, *ibid.*, 1948, **70**, 180). During some synthetic work, we treated 3 : 4-dihydro-6 : 7-dimethoxy-1-(3-methoxy-2-nitrobenzyl)*iso*quinoline with hot methanolic potassium hydroxide. From the warm solution, a yellow crystalline material separated, which was not the expected 1-benzoyl*iso*quinoline derivative.

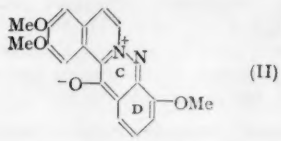
This product, designated A, had the molecular formula $C_{19}H_{16}O_4N_2$ and contained three methoxyl groups. It did not react with stannous chloride in boiling hydrochloric acid, nor did it yield a carbonyl derivative; it was unaffected by sodium borohydride, acetic anhydride, phosphorus pentachloride, hydrogen at 60 lb. in the presence of Adams catalyst in alcohol, or by hot concentrated potassium hydroxide solution, and it did not reduce Fehling's or Tollens's reagent. It was insoluble in cold 4N- but dissolved in hot 10N-hydrochloric acid. From this solution an orange-red hydrochloride crystallised on cooling, and this was also obtained by means of hydrogen chloride in benzene; in water it regenerated the original compound. Treatment of compound A with methyl iodide under pressure yielded a monomethiodide.

It was then of interest to see if other closely related compounds behaved similarly on treatment with hot methanolic potassium hydroxide. From 1-(α-hydroxy-3-methoxy-2-nitrobenzyl)-6 : 7-dimethoxy*iso*quinoline a small amount of 6 : 7-dimethoxy-1-(3-methoxy-2-nitrobenzoyl)*iso*quinoline was obtained, the original compound being mostly recovered. 6 : 7-Dimethoxy-1-(3-methoxy-2-nitrobenzoyl)*iso*quinoline was unaffected by hot methanolic potassium hydroxide, but yielded compound A on reduction with tin and acetic acid or with excess of sodium borohydride in warm methanol.

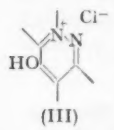
Analogy with the reduction of *o*-nitroacetophenone (Bamberger and Elger, *Ber.*, 1903, **36**, 1617) and *o*-nitrobenzophenone (Bamberger and Lindberg, *Ber.*, 1909, **42**, 1723) to

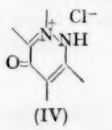
5-methyl- and 5-phenyl-3 : 4-benz*iso*oxazole by tin and acetic acid suggested that compound A might be a benz*iso*oxazole derivative (I). However, 3 : 4-benz*iso*oxazoles are unstable to alkali. 3 : 4-Benz*iso*oxazole itself is converted by dilute sodium hydroxide solution into anthranilic acid (Friedlaender and Henriques, *Ber.*, 1882, **15**, 2106) and 5-methyl-3 : 4-benz*iso*oxazole into *o*-aminoacetophenone (Bamberger, *Ber.*, 1909, **42**,

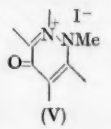


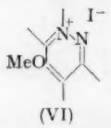


1668). Besides, these compounds are powerful reducing agents giving positive reactions with Fehling's and Tollens's reagents. Structure (I) cannot therefore be valid for compound A. The only other alternative which can be advanced is (II). The ultra-violet absorption spectrum indicated the presence of a highly conjugated system. The infra-red absorption spectrum showed that NH, OH, CO, and NO_2 functions were not present. The infra-red absorption spectrum of the hydrochloride showed presence of an NH or OH function (2·96 μ) and absence of a CO function. On this basis, the hydrochloride should be assigned structure (III), although the hydrochloride would normally have been expected to be (IV). The methiodide showed a strong absorption at 5·86 μ and should therefore be assigned structure (V); however, its methoxyl content corresponded more closely to four methoxyl groups, which indicates structure (VI) for the methiodide; the reason for this anomaly is not evident.

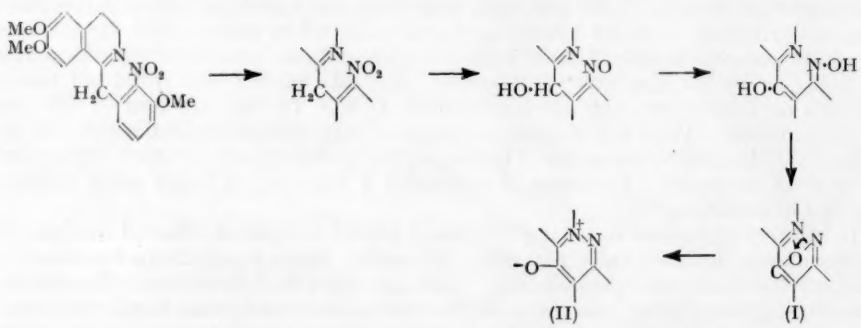








A compound (II) could arise from 3 : 4-dihydro-6 : 7-dimethoxy-1-(3-methoxy-2-nitrobenzyl)*iso*quinoline by the annexed reactions. Similarly, the benz*iso*oxazole (I) is probably the intermediate in the reduction of 6 : 7-dimethoxy-1-(3-methoxy-2-nitrobenzoyl)*iso*quinoline to (II). The formation of the tetracyclic structure of type (II) seems to be a general reaction of 3 : 4-dihydro-1-2′-nitrobenzyl*iso*quinolines with hot methanolic potassium hydroxide: 3 : 4-dihydro-1-(3-methoxy-2-nitrobenzyl)-6 : 7-



methylenedioxy-, 3 : 4-dihydro-6 : 7-dimethoxy-1-2′-nitrobenzyl-, 3 : 4-dihydro-1-(3 : 4-dimethoxy-2-nitrobenzyl)-6 : 7-dimethoxy-, and 3 : 4-dihydro-1-2′-nitrobenzyl-*iso*quinoline all yielded products having four hydrogen atoms and one oxygen atom less than the initial compound. The ultra-violet absorption spectra of these products were closely similar to

that of compound A (see Table). The products were obtained in varying yields which seemed to be influenced by the nature of the substitution in the benzyl portion of the molecule.

In the oxidation of 3 : 4-dihydro-6 : 7-dimethoxy-1-(3-methoxy-2-nitrobenzyl)*iso*quinoline with methanolic potassium hydroxide, three other products besides compound A were isolated. One of these was 3 : 4-dihydro-6 : 7-dimethoxy*iso*carbostyril (Späth and

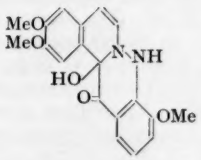
Absorption maxima (mμ) *of products from substituted* 1-*benzyl*-3 : 4-*dihydro*isoquinolines *by methanolic potassium hydroxide.*

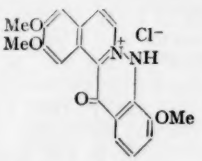
Subst. in benzyl group	Subst. in *iso*quinoline ring	Formula of product	$\lambda_{max.}$	log ε	$\lambda_{max.}$	log ε	$\lambda_{max.}$	log ε
3-OMe-2-NO_2	6 : 7-$(OMe)_2$	$C_{19}H_{16}O_4N_2$ †	225	4·61	262 *	4·39	385	4·21
2-NO_2	6 : 7-$(OMe)_2$	$C_{18}H_{14}O_3N_2$	221	4·61	252	4·56	380	4·32
3-OMe-2-NO_2	6 : 7-O_2CH_2	$C_{18}H_{12}O_4N_2$	232	4·57	262 *	4·37	385	4·22
3 : 4-$(OMe)_2$-2-NO_2	6 : 7-$(OMe)_2$	$C_{20}H_{18}O_5N_2$	232	4·55	262 *	4·37	383	4·07
2-NO_2	—	$C_{16}H_{10}ON_2$	245	4·31	275	3·68	370	4·23

* Inflexion. † Substance A.

Dobrowsky, *Ber.*, 1925, **58**, 1274). A second, m. p. 205—207°, was isolated in quantity too small for further investigation. A third, designated B, had the molecular formula $C_{19}H_{18}O_5N_2$. This was basic, but salt formation with hydrochloric acid or picric acid involved elimination of a molecule of water, yielding salts isomeric with the corresponding salts of compound A. The ultra-violet absorption spectra of the compounds A and B differed. The infra-red absorption spectrum of compound B showed the presence of a carbonyl group (6·15 μ) and more than one NH or OH group (2·75, 2·88, 2·97, 3·13 μ);

(VII)





(VIII)

the infra-red absorption spectrum of its hydrochloride showed the presence of a CO group (6·08 μ), an NH or OH group (2·87, 3·03 μ), and a salt structure (4·43, 4·97, 5·05 μ). On this basis, compound B and its hydrochloride are assigned structures (VII) and (VIII).

Attempts to confirm the structures proposed are in progress.

Experimental

Analyses are partly by Mr. S. Selvavinayagam.

Action of Methanolic Potassium Hydroxide.—(a) *On* 3 : 4-*dihydro*-6 : 7-*dimethoxy*-1-(3-*methoxy*-2-*nitrobenzyl*)iso*quinoline*. A solution of the base (Govindachari and Pai, *J. Org. Chem.*, 1953, **18**, 1352) (4·5 g.) in 10% methanolic potassium hydroxide (75 ml.) was refluxed on a water-bath for 8 hr., during which the originally clear brown solution deposited yellow crystals. The solution was cooled and the precipitate was filtered off and washed with methanol (filtrate A). Crystallisation of the residue from alcohol yielded *compound A* as yellow needles (1·7 g.), m. p. 179° [Found : C, 67·7, 67·8; H, 4·5, 4·7; N, 8·4, 8·3; OMe, 25·7%; *M*, ebullioscopically in benzene, 340, 349. $C_{19}H_{16}O_4N_2$ requires C, 67·9; H, 4·8; N, 8·3; OMe, 27·7%; *M*, 336].

The *hydrochloride*, prepared by passing dry hydrogen chloride into a solution of compound A in benzene, crystallised from alcohol–ether as yellow needles, m. p. 178° (decomp.). A red form was obtained by cooling a solution of the base in concentrated hydrochloric acid, but crystallisation from alcohol–ether yielded the yellow form, m. p. 178° (decomp.) (Found : C, 60·9; H, 4·3; N, 7·7; Cl, 9·7. $C_{19}H_{17}O_4N_2Cl$ requires C, 61·2; H, 4·6; N, 7·5; Cl, 9·5%). The *picrate*, prepared in benzene, crystallised from benzene as yellow needles, m. p. 205° (decomp.) (Found :

C, 52·5; H, 3·1; N, 12·7. $C_{25}H_{19}O_{11}N_5$ requires C, 53·1; H, 3·4; N, 12·4%). The compound A (0·5 g.) was heated in chloroform (5 ml.) with methyl iodide (5 ml.) at 100° for 18 hr. The solvent was then removed and the residue was dissolved in boiling alcohol (75 ml.). The solution was concentrated to 10 ml., then cooled, the amorphous precipitate removed, and the filtrate diluted with ether to turbidity. Pale yellow needles of the *methiodide* were obtained which after recrystallisation from alcohol–ether melted at 178° (Found: C, 49·7; H, 4·4; N, 5·8; OMe, 29·2. $C_{20}H_{19}O_4N_2I$ requires C, 50·2; H, 4·0; N, 5·9; 4OMe, 25·9, 3OMe, 19·5%).

The methanolic filtrate A was evaporated to dryness and a solution of the residue in benzene was repeatedly extracted with N-hydrochloric acid (benzene layer B). The acid extract was rendered alkaline and extracted with benzene and the solvent removed after drying (K_2CO_3). The residue in a small volume of benzene was passed through a column of alumina, and the column washed with benzene (500 ml.). The eluate yielded a solid (0·5 g.) which was repeatedly extracted with light petroleum (b. p. 40—60°); the soluble portion (0·05 g.) melted at 205—207° (Found: C, 51·9; H, 7·0; N, 7·1%); the insoluble portion, *compound* B, on recrystallisation from dilute alcohol, gave yellow needles, m. p. 117—118° (Found: C, 64·7; H, 5·6; N, 8·0; OMe, 24·1. $C_{19}H_{18}O_5N_2$ requires C, 64·4; H, 5·1; N, 7·9; 3OMe requires OMe, 26·3%). The *hydrochloride*, prepared as above, and crystallised from alcohol, had m. p. 195° (decomp.) (Found: C, 61·4; H, 5·2; N, 7·8. $C_{19}H_{17}O_4N_2Cl$ requires C, 61·2; H, 4·6; N, 7·5%). The *picrate* prepared in benzene and crystallised from benzene, had m. p. 187° (decomp.) (Found: C, 53·1; H, 3·5; N, 12·3. $C_{25}H_{19}O_{11}N_5$ requires C, 53·1; H, 3·4; N, 12·4%).

The benzene layer B was dried (Na_2SO_4), concentrated, and poured on a column of alumina, which was then washed with dry benzene. A yellow band was rapidly removed. Evaporation of the eluate from this zone gave compound A, m. p. 179° (0·1 g.). Subsequent elution with benzene containing 2% of alcohol gave a colourless solid, crystallising from benzene in plates (0·05 g.), m. p. 171—172° alone or mixed with 3:4-dihydro-6:7-dimethoxy*iso*carbostyril (Found: C, 63·5; H, 6·3; N, 6·8. Calc. for $C_{11}H_{13}O_3N$: C, 63·8; H, 6·3; N, 6·8%).

(b) *On* 3:4-*dihydro*-1-(3-*methoxy*-2-*nitrobenzyl*)-6:7-*methylenedioxy*isoquinoline. The base (0·3 g.) (Barger and Schlittler, *Helv. Chim. Acta*, 1932, **15**, 381) was refluxed with a solution of potassium hydroxide (3 g.) in methanol (100 ml.) for 12 hr. The *product* that separated was filtered off, after cooling, and crystallised from alcohol as orange needles (0·1 g.), m. p. 208° (Found: C, 67·4, 67·3; H, 3·8, 3·6; N, 9·0. $C_{18}H_{12}O_4N_2$ requires C, 67·5; H, 3·7; N, 8·8%).

(c) *On* 3:4-*dihydro*-1-(3:4-*dimethoxy*-2-*nitrobenzyl*)-6:7-*dimethoxy*isoquinoline. The base (1 g.) (Gulland and Haworth, *J.*, 1928, 1834) was refluxed with a solution of potassium hydroxide (3 g.) in methanol (50 ml.) for 10 hr. The *product* that separated crystallised from alcohol as yellow needles (0·15 g.), m. p. 150° (Found: C, 65·1; H, 5·0; N, 7·6. $C_{20}H_{18}O_5N_2$ requires C, 65·6; H, 4·9; N, 7·7%).

(d) *On* 3:4-*dihydro*-6:7-*dimethoxy*-1-2′-*nitrobenzyl*isoquinoline. The base (2 g.) (Gulland and Haworth, *J.*, 1928, 581) was heated under reflux with a solution of potassium hydroxide (6 g.) in methanol (100 ml.) for 12 hr. The solvent was then removed and the residue partitioned between benzene and N-hydrochloric acid. The benzene layer was washed with water, dried, concentrated to a small volume, and poured on alumina. Elution with benzene yielded a *product* which crystallised from alcohol in yellow needles (0·01 g.), m. p. 184—185° (Found: C, 71·0; H, 4·7; N, 9·3. $C_{18}H_{14}O_3N_2$ requires C, 70·6; H, 4·6; N, 9·2%). Elution with benzene containing 1% of alcohol then gave plates (0·17 g.) (from benzene), m. p. 172° alone or mixed with 3:4-dihydro-6:7-dimethoxyisocarbostyril.

The hydrochloric acid extract (above) was rendered alkaline and extracted with benzene. The sticky material recovered from the benzene was chromatographed on alumina and yielded a greenish-yellow *substance* (0·15 g.), crystallising from benzene in needles, m. p. 166° (Found: C, 70·1; H, 5·6; N, 9·2. $C_{18}H_{16}O_3N_2$ requires C, 70·1; H, 5·2; N, 9·1%). This is probably a dihydro-derivative of the compound $C_{18}H_{14}O_3N_2$, m. p. 184°.

(e) *On* 3:4-*dihydro*-1-2′-*nitrobenzyl*isoquinoline. This compound has not been reported previously. Kay and Pictet (*J.*, 1913, **103**, 947) and Gadamer, Oberlin, and Schoeler (*Arch. Pharm.*, 1925, **263**, 81) reported that it could not be obtained from *o*-nitrophenyl-*N*-phenethylacetamide, but the following procedure was successful. The amide (Kay and Pictet, *loc. cit.*) (2 g.) was refluxed in dry toluene (80 ml.) with phosphoric oxide (12 g.) for 2 hr., during which more phosphoric oxide (13 g.) was added in portions. The mixture was then cooled, the excess of oxide was decomposed by crushed ice, and the aqueous layer separated and extracted with ether to remove non-basic material. The aqueous solution was then cooled and rendered alkaline and the liberated 3:4-*dihydro*-1-2′-*nitrobenzyl*isoquinoline extracted with ether, purified by one more passage through acid, and obtained after crystallisation from alcohol as

tan-coloured needles (0·49 g.), m. p. 115—116° (Found : C, 72·0; H, 5·3; N, 10·8. $C_{16}H_{14}O_2N_2$ requires C, 72·2; H, 5·3; N, 10·5%).

The above base (0·9 g.) was heated with methanolic potassium hydroxide (10%; 20 ml.) for 12 hr. The solvent was then removed and the residue was taken up in benzene. Basic material was removed by dilute hydrochloric acid and the sticky mass which was recovered from the benzene layer was purified by chromatography on alumina. Elution with benzene yielded a *product* (0·2 g.) which, crystallised from alcohol, had m. p. 106—107° (Found : C, 78·5; H, 3·9; N, 11·5. $C_{16}H_{10}ON_2$ requires C, 78·1; H, 4·1; N, 11·4%).

Reduction of 6 : 7-*Dimethoxy*-1-(3-*methoxy*-2-*nitrobenzoyl*)iso*quinoline*.—(a) *With tin and acetic acid*. A solution of 6 : 7-dimethoxy-1-(3-methoxy-2-nitrobenzoyl)*iso*quinoline (0·6 g.) (Govindachari and Nagarajan, *J.*, 1954, 2537) in boiling glacial acetic acid (6 ml.) was treated with tin foil (0·3 g.), then diluted with water (100 ml.) and repeatedly extracted with benzene. The extract was washed with water, dried (Na_2SO_4), concentrated to a small volume, and poured on alumina. Elution with benzene removed a yellow band rapidly, which gave compound A (0·15 g.), m. p. 179° (from alcohol).

(b) *With sodium borohydride in hot methanol*. The base (0·5 g.) in absolute methanol (30 ml.) was heated with sodium borohydride (1 g.) on a steam-bath for 6 hr. On cooling, a few crystals separated. These, recrystallised from alcohol, had m. p. 228—231° (Found : C, 66·0; H, 5·2; N, 8·7%). This *substance* was not further characterised or identified.

The filtrate was diluted with water (200 ml.) and extracted with benzene. The extract was concentrated to 10 ml. and poured on alumina. Washing with benzene (500 ml.) removed a yellow band from which compound A (0·15 g.) was isolated as yellow needles, m. p. 179° (from alcohol).

Subsequent elution with benzene containing 1% of alcohol gave 1-(α-hydroxy-3-methoxy-2-nitrobenzyl)-6 : 7-dimethoxy*iso*quinoline (Govindachari and Nagarajan, *loc. cit.*). This was the sole product if the reduction was carried out with cooling, below 30°.

Reduction of 6 : 7-*Dimethoxy*-1-2′-*nitrobenzoyl*iso*quinoline with Tin and Acetic Acid*.—This *base* was prepared by oxidation of 3 : 4-dihydro-6 : 7-dimethoxy-1-2′-nitrobenzyl*iso*quinoline (1 g.) with potassium dichromate (2 g.) in hot 70% acetic acid (5 ml.) for 1 hr. The material that separated was filtered off after cooling, and crystallised from alcohol as yellow plates, m. p. 200° (decomp.) (Found : C, 63·9; H, 4·4; N, 8·5. $C_{18}H_{14}O_5N_2$ requires C, 63·9; H, 4·1; N, 8·3%).

A solution of this base (0·3 g.) in boiling acetic acid (7 ml.) was treated with tin foil (0·15 g.). After all the tin had dissolved, the solution was diluted with water (100 ml.). The yellow precipitate was filtered off and recrystallised from alcohol, giving yellow flakes (0·2 g.), m. p. 185—187°, identical with the product $C_{18}H_{14}O_5N_2$ obtained by use of methanolic potassium hydroxide.

We are grateful to Professor A. R. Todd, F.R.S., and Prof. Roger Adams for valuable suggestions and for infra-red measurements, and to Dr. R. N. Haszeldine and Dr. E. J. Corey for interpretation of infra-red absorption spectra. We thank Dr. B. R. Pai for experimental assistance and helpful discussions and the Government of India for the award of a studentship to one of us (K. N.).

PRESIDENCY COLLEGE, MADRAS. [*Received, March 22nd*, 1954.]

Steroids and Walden Inversion. Part XVII. The Configuration of ψ-Cholesterol and the Attempted Preparation of 4β-Methoxy-5 : 7-cyclocholestane.*

By R. J. W. Cremlyn, R. W. Rees, and C. W. Shoppee.

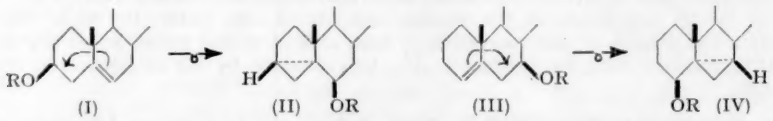
[Reprint Order No. 5495.]

ψ-Cholesterol, by hydrogenation, gives cholestan-7β-ol; ψ-cholesterol is therefore cholest-4-en-7β-ol. It is not epimerised by hot sodium amyloxide or sodium ethoxide.

ψ-Cholesterol with phosphorus pentachloride gives 7β-chlorocholest-4-ene with retention of configuration at $C_{(7)}$; although the chloride could not be obtained crystalline, the configuration of the 7-chlorine atom is established by hydrogenation to 7β-chlorocholestane, followed by acetolysis, and alkaline hydrolysis, to afford cholestan-7α-ol.

Attempts to convert ψ-cholesteryl toluene-*p*-sulphonate into 4β-methoxy-5 : 7-*cyclo*cholestane were unsuccessful; methanolysis in the presence or absence of potassium acetate gave a non-crystalline methyl ether, which appeared to be identical with ψ-cholesteryl methyl ether, prepared from ψ-cholesterol by methylation with potassium and methyl iodide. Hydrolysis of ψ-cholesteryl toluene-*p*-sulphonate occurs on alkaline aluminium oxide with retention of configuration at $C_{(7)}$ to regenerate ψ-cholesterol; a small proportion of cholesta-4 : 6-diene is also produced.

The general symmetry of the 3- and the 7-position in the steroid nucleus suggests that the conversion of 3β-substituted Δ^5-steroids (I) into 6β-substituted 3 : 5-*cyclo*steroids (II) (cf. Shoppee and Summers, *J.*, 1952, 3361, for a summary of earlier work) might be paralleled by transformation of 7β-substituted Δ^4-steroids (III) into 4β-substituted 5 : 7-*cyclo*steroids (IV). We therefore commenced a study of the reactions of ψ-cholesterol.



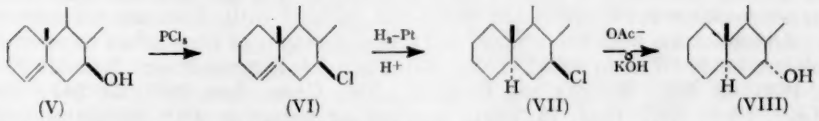
ψ-Cholesterol, m. p. 116°, $[\alpha]_D$ + 58°, $\lambda_{max.}$ 211 mμ, log ε 3·51, was obtained 40 years ago by reduction of cholesta-3 : 5-dien-7-one with sodium and ethanol by Windaus and Resau (*Ber.*, 1915, **48**, 851), who characterised it by preparation of the benzoate. Since the 3 : 5-*cyclo*steroid rearrangement fails with 3α-substituted Δ^5-steroids (Evans and Shoppee, *J.*, 1953, 540), an essential preliminary was to show that the hydroxyl group in ψ-cholesterol is β-orientated. ψ-Cholesterol, characterised as the acetate and 3 : 5-dinitrobenzoate, was hydrogenated with platinum in ethyl acetate in the presence of a trace of perchloric acid (cf. Hershberg *et al.*, *J. Amer. Chem. Soc.*, 1951, **73**, 1144) to give cholestan-7β-ol (Cremlyn and Shoppee, *J.*, 1954, 3515); this establishes the β-configuration of the hydroxyl group in ψ-cholesterol (V).

This assignment (7β-OH; equatorial †) is consistent with the fact that ψ-cholesterol is unchanged by treatment with hot sodium–amyl alcohol or with sodium ethoxide at 180°. Attempted confirmation by the method of molecular-rotation differences fails, probably owing to vicinal action. Calculated values of $[M]_D$ for ψ-cholesterol and *epi*-

* Part XVI, *J.*, 1954, 3515.

† Ring B in cholest-4-ene is a strained chair-form; carbon atoms $C_{(10)}$, $C_{(5)}$, and $C_{(6)}$ are coplanar, lying in the general plane of the tetracyclic system, and the bond axis $C_{(7)}$–$C_{(8)}$ is no longer parallel to the bond axis $C_{(10)}$–$C_{(5)}$, but inclined thereto with $C_{(7)}$ lying a little behind the plane containing $C_{(10)}$, $C_{(5)}$, $C_{(6)}$, and $C_{(8)}$, so that substituents at $C_{(7)}$ deviate only slightly from normal equatorial and axial conformations as in *cyclo*hexane. Ring A has the "half-chair" conformation as in *cyclo*hexene with four contiguous coplanar carbon atoms [$C_{(3)}$, $C_{(4)}$, $C_{(5)}$, and $C_{(10)}$] (cf. Barton, Cookson, Klyne, and Shoppee, *Chem. and Ind.*, 1954, 21).

ψ-cholesterol are +371° * and +190°,* or +351° † and +179°,† whereas the observed value for ψ-cholesterol is +233°, which suggests that the 7-hydroxyl group is α-orientated; the calculated values for the epimeric acetates are +456° † and +104°,† whereas the observed value for ψ-cholesteryl acetate is +281°.

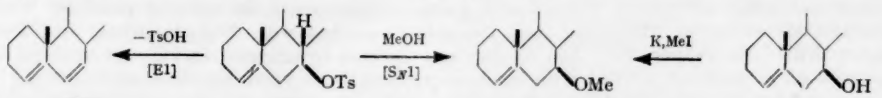


(V) (VI) (VII) (VIII)

It is now generally agreed that intervention of the π-electrons of the 5 : 6-double bond at $C_{(5)}$ (as I) leads, according to the experimental conditions, (*a*) to replacement with retention of configuration at $C_{(3)}$, or (*b*) to rearrangement with inversion at $C_{(3)}$ and production of a 3 : 5-*cyclo*steroid as (II). It seemed accordingly desirable next to examine the stereochemical course of replacement of hydroxyl by chlorine in ψ-cholesterol.

Windaus and Resau (*loc. cit.*) by treatment of ψ-cholesterol with phosphorus pentachloride obtained a non-crystalline chloride, which they reduced with sodium–ethanol to cholest-4-ene. Similarly, we obtained ψ-cholesteryl chloride (VI) as an oil, $[\alpha]_D$ +71°, $\lambda_{max.}$ 212, log ε 3·44 (in Et_2O), which by hydrogenation with platinum–ethyl acetate–perchloric acid (trace) gave 7β-chlorocholestane (VII), m. p. 65—68°, $[\alpha]_D$ +77° (Cremlyn and Shoppee, following paper); this by acetolysis and subsequent alkaline hydrolysis gave cholestan-7α-ol (VIII) (Cremlyn and Shoppee, *loc. cit.*) accompanied by cholest-7-ene. These results show that the replacement (V ⟶ VI) occurs with retention of configuration. By use of thionyl chloride ψ-cholesterol gave a non-crystalline and somewhat less pure preparation of ψ-cholesteryl chloride, $[\alpha]_D$ +54°, $\lambda_{max.}$ 211 mμ, log ε 3·27 (in Et_2O).

ψ-Cholesteryl toluene-*p*-sulphonate (X), when refluxed with methanol in the presence of potassium acetate, gave (*a*) cholesta-4 : 6-diene (IX), m. p. 88°, $[\alpha]_D$ +4°, $\lambda_{max.}$ 238 mμ, log ε 4·2, formed by elimination of toluene-*p*-sulphonic acid, and (*b*) an oil, $[\alpha]_D$ +70°, $\lambda_{max.}$ 211 mμ, log ε 3·41, which we regard as ψ-cholesteryl methyl ether (XI) rather than as the 5 : 7-*cyclo*cholestane derivative (IV; R = Me) on the following grounds. First, methanolysis of ψ-cholesteryl toluene-*p*-sulphonate in the absence of potassium acetate furnished the same two products; secondly, the methyl ether by treatment with hydrochloric–acetic acid at 15° failed to rearrange to ψ-cholesteryl chloride (VI) as would be expected by analogy with the ready conversion of 6β-methoxy-3 : 5-*cyclo*cholestane into cholesteryl chloride (Beynon, Heilbron, and Spring, *J.*, 1936, 907); thirdly, methylation of ψ-cholesterol with potassium and methyl iodide gave a non-crystalline methyl ether



(IX) (X) (XI) (V)

with the same physical characteristics. We have thus been unable to realise the rearrangement (III ⟶ IV); a probable contributory factor is the greater rigidity of ring B in (III), resulting from *trans*-fusion with ring C, as compared with ring A in (I). We are examining the reaction of the toluene-*p*-sulphonate (X) with other alcohols, *e.g.*, 4-bromobenzyl alcohol, in the hope of obtaining crystalline analogues of (XI) or (IV); an alternative route to compounds of type (IV) using 4-oxocholestan-7β-yl toluene-*p*-sulphonate or halides is also being explored.

We have observed that, whilst ψ-cholesteryl toluene-*p*-sulphonate (X) in pentane solution is unaltered by passage through a column of neutralised aluminium oxide, use

* Calculated as follows: [M_D (cholestane-3β : 7β-diol) = +214°] − [ΔO : 3β = +2°] + [ΔE4 = +159°] = +371°; [M_D (cholestane-3β : 7α-diol) = +33°] − [ΔO : 3β = +2°] + [ΔE4 = +159°] = +190° (cf. Barton and Klyne, *Chem. and Ind.*, 1948, 755).

† The contributions for ΔO : 7β and ΔO : 7α in A/B-*trans*- and A/B-*cis*-systems are averaged (7β = +103°, 7α = −69°) and added to the molecular rotation for cholest-4-ene + 248°. The contributions for ΔA : 7β and ΔA : 7α are similarly averaged (7β = +208°, 7α = −144°) and added.

of alkaline aluminium oxide leads to hydrolysis (70%) with intervention of the π-electrons of the 4 : 5-double bond and retention of configuration at $C_{(7)}$, to regenerate ψ-cholesterol (V), and to an elimination reaction (*E*1) (~12%) whereby the intermediate carbonium ion affords cholesta-4 : 6-diene (IX).

An attempt was made to prepare *epi*-ψ-cholesterol. ψ-Cholesterol was converted into the non-crystalline 4ξ : 5ξ-dibromide, which was oxidised with chromium trioxide–acetic acid; debromination with zinc–ethanol and chromatography of the product on neutralised aluminium oxide failed to afford cholest-4-en-7-one (cf. Butenandt and Schmidt-Thomé, *Ber.*, 1936, **69**, 882; Ruzicka and Bosshard, *Helv. Chim. Acta*, 1937, **20**, 244; Fieser, *J. Amer. Chem. Soc.*, 1953, **75**, 5421) required for reduction with lithium aluminium hydride or sodium borohydride, and furnished cholest-5-en-7-one. This conversion of an unconjugated ketone into the conjugated isomeride may have been induced by the specimen of aluminium oxide used, and may be compared with the conversion of cholest-5- into cholest-4-en-3-one (Shoppee and Summers, *J.*, 1950, 687; Birch, *ibid.*, p. 2325).

Experimental

For general experimental directions see *J.*, 1954, 3515. $[\alpha]_D$ were determined in $CHCl_3$ and ultra-violet absorption spectra were determined with an SP. 500 Unicam spectrophotometer with corrected scale in EtOH, unless otherwise stated. Neutralised aluminium oxide was prepared according to the procedure of Reichstein and Shoppee (*Discuss. Faraday Soc.*, 1949, **7**, 305).

ψ-Cholesterol. This was prepared from 7-oxocholesteryl acetate by alkaline hydrolysis, dehydration to cholesta-3 : 5-dien-7-one, and reduction thereof with sodium–propan-1-ol in 65% yield (cf. Windaus and Resau, *Ber.*, 1915, **48**, 851). It had m. p. 116°, $[\alpha]_D$ +60° (*c*, 0·81), $\lambda_{max.}$ 211 mμ, log ε 3·51, after recrystallisation from acetone–methanol and was characterised by preparation (acetic anhydride–pyridine at 15°) of the *acetate*, m. p. 63—64°, $[\alpha]_D$ +65° (*c*, 1·24), after recrystallisation from acetone–methanol [Found (after drying at 40°/0·01 mm. for 4 hr.): C, 81·0; H, 11·1. $C_{29}H_{48}O_2$ requires C, 81·2; H, 11·3%], and the benzoate, m. p. 156°, $[\alpha]_D$ +99°; also by preparation [3 : 5-dinitrobenzoyl chloride–benzene–pyridine at 15° (cf. Reichstein, *Helv. Chim. Acta*, 1926, **9**, 799)] of the 3 : 5-*dinitrobenzoate*, m. p. 166—167°, $[\alpha]_D$ +107° (*c*, 3·38), after two recrystallisations from acetone [Found (after drying at 20°/0·01 mm. for 12 hr.): C, 70·2; H, 8·3. $C_{34}H_{48}O_6N_2$ requires C, 70·3; H, 8·3%], and by preparation of the *toluene*-p-*sulphonate*, m. p. 135—136° (decomp. to a red melt), $[\alpha]_D$ +21° (*c*, 1·0), after recrystallisation from acetone [Found (after drying at 90°/0·01 mm. for 3 hr.): C, 75·4; H, 9·65. $C_{34}H_{52}O_3S$ requires C, 75·5; H, 9·7%].

ψ-Cholesterol (172 mg.) was dissolved in amyl alcohol (30 c.c.) and sodium added to the boiling solution until no more would dissolve. After refluxing for 6 hr., the solution was cooled and, after addition of ethanol and water, evaporated under reduced pressure. The product was extracted with ether, and the extract washed with 2N-hydrochloric acid and water, dried, and evaporated. The residue was purified by chromatography on aluminium oxide (6 g.) in pentane; elution with benzene–pentane (1 : 4) yielded ψ-cholesterol (150 mg.), m. p. 116°, after recrystallisation from acetone–methanol. Similarly, ψ-cholesterol (100 mg.) after treatment with 1·2N-ethanolic sodium ethoxide at 180° for 80 hr. was recovered unchanged (90 mg.), m. p. 116° after recrystallisation from acetone–methanol.

Cholestan-7β-ol from ψ-Cholesterol.—ψ-Cholesterol (470 mg.), in pure ethyl acetate (25 c.c.) containing perchloric acid (60%; 0·1 c.c.), was shaken with platinum oxide (50 mg.) in hydrogen; allowing for reduction of the catalyst, 27·5 c.c. (1 mol.) were taken up in 5 min., whereafter absorption ceased. The product, obtained by filtration, washing with 2N-sodium carbonate, then with water, drying, and vacuum-evaporation, was chromatographed on aluminium oxide (15 g.) in pentane. Elution with pentane (3 × 50 c.c.) gave some uncrystallisable material, but use of benzene–pentane (1 : 9; then 1 : 4, 5 × 50 c.c.) afforded cholestan-7-β-ol (383 mg.), m. p. 115°, $[\alpha]_D$ +45° (*c*, 1·305), after recrystallisation from methanol, giving no m. p. depression with authentic cholestan-7β-ol and no colour with tetranitromethane–chloroform.

ψ-Cholesteryl Chloride.—(*a*) ψ-Cholesterol (1·5 g.; dried by azeotropic distillation with benzene) was treated with freshly sublimed phosphorus pentachloride (3·5 g.) in chloroform (70 c.c.) in the presence of calcium carbonate (2·2 g.) during 45 min. at 0°. The mixture was shaken for 2 hr. at 0°, then for a further 1·5 hr. at 15°, and set aside overnight. The usual

working up gave a yellow oil (1·6 g.), which was chromatographed on neutralised aluminium oxide (40 g.) in pentane; elution with pentane (4 × 250 c.c.) yielded *ψ-cholesteryl chloride* (1·36 g.), $[\alpha]_D$ +71° (*c*, 1·97), $\lambda_{max.}$ 212 mμ, log ε 3·44 in Et_2O (Found: Cl, 8·0. $C_{27}H_{45}Cl$ requires Cl, 8·7%), as a colourless oil which did not crystallise. A second preparation showed the same physical constants. The chloride (1·35 g.) was hydrogenated with platinum oxide in ethyl acetate containing one drop of 60% perchloric acid; after absorption ceased, the catalyst was filtered off, ethyl acetate largely removed in a vacuum, and the residue worked up in the usual way. The product was chromatographed on neutralised aluminium oxide (40 g.) in pentane; elution with pentane (2 × 200 c.c.) furnished a product consisting essentially of 7β-*chlorocholestane* (965 mg.) as a colourless oil,* $[\alpha]_D$ +71° (*c*, 4·82) (Found: Cl, 7·9. $C_{27}H_{47}Cl$ requires 8·7%) giving no colour with tetranitromethane. Further elution with pentane (2 × 100 c.c.) gave (i) a colourless oil (140 mg.), which gave no colour with tetranitromethane and partially crystallised on prolonged cooling to give, after drainage on porous porcelain and two recrystallisations from acetone, a small quantity of an incompletely pure *dichloro-compound*, m. p. 88—90°, $[\alpha]_D$ +103° (*c*, 3·12) (Found: Cl, 18·9. $C_{27}H_{46}Cl_2$ requires Cl, 16·1%), and (ii) a colourless unsaturated oil (77 mg.) giving a strong yellow colour with tetranitromethane. The specimen of 7β-chlorocholestane (785 mg.) was heated with freshly fused potassium acetate (7·5 g.) in acetic acid (15 c.c.) with exclusion of moisture for 48 hr. The cooled mixture was poured into 2N-sodium carbonate (50 c.c.), and the product, isolated in the usual way, refluxed with 4% methanolic potassium hydroxide (60 c.c.) for 1 hr. After addition of a little water, passage of carbon dioxide, and evaporation in a vacuum, the hydrolysis product was worked up in the usual way, and the resultant oil (756 mg.) chromatographed on neutralised aluminium oxide (21 g.) in pentane. Elution with pentane (4 × 75 c.c.) gave an oil (302 mg.), $[\alpha]_D$ +26°, which solidified and yielded cholest-7-ene, m. p. 81—83°, $[\alpha]_D$ +14° (*c*, 1·45), after three recrystallisations from acetone; elution with benzene–pentane (1 : 1; 8 × 75 c.c.) gave cholestan-7α-ol (91 mg.), m. p. and mixed m. p. 97—98°, $[\alpha]_D$ +6° (*c*, 1·07), after recrystallisation from acetone. Further elution with benzene–pentane, benzene, and ether–benzene failed to furnish cholestan-7β-ol and gave only uncrystallisable yellow oils (111 mg.).

(*b*) *ψ*-Cholesterol (350 mg.) was refluxed with thionyl chloride (2·5 c.c.) with exclusion of moisture for 3 hr.; the cooled mixture was poured into ice-water and worked up in the usual way, to give an oil (380 mg.) which was chromatographed on neutralised aluminium oxide (20 g.) prepared in pentane. Elution with pentane (2 × 200 c.c.) gave an oil (50 mg.) consisting largely of *ψ*-cholesteryl chloride, $[\alpha]_D$ +54° (*c*, 2·69), $\lambda_{max.}$ 211 mμ, log ε 3·27 in Et_2O; elution with benzene–pentane (1 : 4, 3 × 200 c.c.) gave *ψ*-cholesterol (320 mg.), m. p. and mixed m. p. 116° after two recrystallisations from acetone.

Methanolysis of ψ-Cholesteryl Toluene-p-*Sulphonate.*—(a) *In presence of potassium acetate.* *ψ*-Cholesteryl toluene-*p*-sulphonate (1 g.) was refluxed with anhydrous potassium acetate (2·8 g.) in methanol (240 c.c.) for 6 hr.; methanol (*ca.* 200 c.c.) was removed under reduced pressure, water added, and the product extracted with ether. The ethereal extract was washed with water, dried, and evaporated completely to yield an oil (760 mg.). Chromatography on aluminium oxide (40 g.) prepared in pentane, and elution with pentane (75 c.c.) gave cholesta-4 : 6-diene, m. p. and mixed m. p. 89—90°, $[\alpha]_D$ +3° (*c*, 1·11), $\lambda_{max.}$ 239 mμ, log ε 4·2 (cf. Eck and Hollingsworth, *J. Amer. Chem. Soc.*, 1941, **63**, 107). Further elution with pentane (5 × 75 c.c.) gave a colourless oil (605 mg.); this was rechromatographed and split into numerous fractions whose ultra-violet absorption spectra were examined. Those fractions with $\lambda_{max.}$ 210 mμ were combined and distilled (short path) at 110°/0·003 mm.; the distillate failed to crystallise, but a solution in acetone–methanol at −80° yielded crystals, which melted between 0° and 10°. 7β-*Methoxycholest-4-ene* (*ψ-cholesteryl methyl ether*) had $[\alpha]_D$ +70° (*c*, 2·48), $\lambda_{max.}$ 211 mμ, log ε 3·39 (Found: C, 83·6; H, 12·0. $C_{28}H_{48}O$ requires C, 83·9; H, 12·1%), and gave a lilac colour in the Rosenheim test only on standing; treatment with concentrated hydrochloric (or hydrobromic) acid in acetic acid at 15° for 40 hr. gave an amorphous product, which was separated by chromatography on aluminium oxide in pentane into seven non-crystalline fractions all giving a negative Beilstein test.

(b) *ψ*-Cholesteryl toluene-*p*-sulphonate (245 mg.) was refluxed with methanol (68 c.c.) for 2½ hr.; the product was an oil with physical constants closely similar to those recorded above for *ψ*-cholesteryl methyl ether.

* Only subsequently was 7β-chlorocholestane obtained crystalline, m. p. 65—68°, $[\alpha]_D$ +77° (cf. Cremlyn and Shoppee, following paper).

(c) ψ-Cholesterol (890 mg.) was refluxed with potassium (500 mg.) in benzene (40 c.c.) for 1 hr.; methyl iodide (20 c.c.) was added and refluxing continued for 3 hr. After cooling, methanol was added to destroy excess of potassium, and the solvents and methyl iodide were removed under reduced pressure; extraction of the residue with pentane and evaporation of the extract gave an oil (880 mg.), which by chromatography gave 7β-methoxycholest-4-ene [700 mg.) as an oil, $[\alpha]_D$ +70° (*c*, 4·18), $\lambda_{max.}$ 211 mμ, log ε 3·41, giving a lilac colour in the Rosenheim test only on standing.

Action of Aluminium Oxide on ψ-Cholesteryl Toluene-p-*Sulphonate*.—The toluene-*p*-sulphonate was recovered unchanged after chromatography on neutralised aluminium oxide in pentane. When the toluene-*p*-sulphonate (170 mg.) was introduced on to a column of aluminium oxide (Spence type H, 200 mesh, activity ~II on the scale of Brockmann and Schodder, *Ber.*, 1941, **74**, 73; 8 g.) and eluted with pentane (4 × 100 c.c.), cholesta-4 : 6-diene (20 mg.), m. p. 88—90°, $[\alpha]_D$ +4° (*c*, 1·1) (Eck and Hollingsworth, *loc. cit.*), was obtained; further elution with benzene–pentane (1 : 1; 4 × 100 c.c.) gave ψ-cholesterol (122 mg.), m. p. and mixed m. p. 116—117° after recrystallisation from acetone–methanol.

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Steroids and Walden Inversion. Part XVIII. The Preparation and Configuration of the Epimeric 7-Chlorocholestanes.*

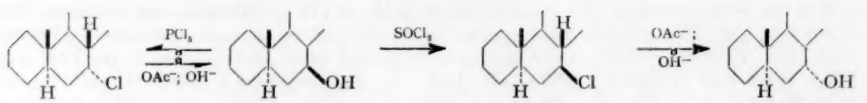
By R. J. CREMLYN and C. W. SHOPPEE.

[Reprint Order No. 5496.]

The epimeric 7-chlorocholestanes have been prepared and their configurations determined by conversion by acetolysis and alkaline hydrolysis into the appropriate cholestan-7-ols. Their behaviour in elimination reactions with pyridine, *s*-collidine, and quinoline has been examined.

IN Part I of this series (Shoppee, *J.*, 1946, 1138) the configurations of the epimeric 3-chlorocholestanes were established. The present paper describes the preparation of the epimeric 7-chlorocholestanes and an examination of their acetolysis products, whereby their configurations have been determined.

Treatment of cholestane-7β-ol (II) with phosphorus pentachloride in chloroform in the presence of calcium carbonate at 0° gave 7α-chlorocholestane (I) (55%) together with some unsaturated material; use of phosphorus pentabromide similarly furnished 7α-bromocholestane, m. p. 109°, $[\alpha]_D$ −20°. The change of sign in the specific rotation of the alcohol (II) and the products of these substitution reactions suggests that inversion of configuration at $C_{(7)}$ has occurred.



(I) M. p. 78°, [−21°] (II) M. p. 113°, [+52°] (III) M. p. 67°, [+77°] (IV) M. p. 98°, [+11°]

(Values in square brackets are $[\alpha]_D$)

Similar treatment of cholestan-7α-ol (IV) with phosphorus pentachloride afforded only unsaturated non-crystalline products. However, treatment of cholestan-7β-ol (II) with thionyl chloride in ether in the presence of calcium carbonate at 0—20° gave a small yield of 7β-chlorocholestane (III), accompanied by cholestan-7β-yl sulphite and much

* Part XVII, preceding paper.

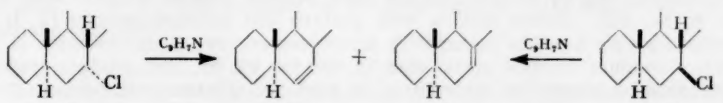
cholest-7-ene; use of thionyl chloride in absence of a solvent and of calcium carbonate first at 20° and then at 75° was more satisfactory and gave 7β-chlorocholestane (III) (59%). The correspondence of sign in the specific rotation of the alcohol (II) and the chloride (III) suggests retention of configuration at $C_{(7)}$.

Whereas the epimeric 3-chlorocholestanes were found to undergo acetolysis only at 180°, the epimeric 7-chlorocholestanes react slowly with 4M-potassium acetate in acetic acid at 140°. Acetolysis of 7α-chlorocholestane (I) gave material which, after alkaline hydrolysis, was separated chromatographically into pure cholestan-7β-ol (II) (15%) unaccompanied by the 7α-epimeride, and cholest-7-ene (78%), m. p. 83°, $[\alpha]_D$ +14°. Conversely, acetolysis of 7β-chlorocholestane (III) gave a product which, after alkaline hydrolysis, furnished pure cholestan-7α-ol (IV) (43%) unaccompanied by the 7β-epimeride, and cholest-7-ene (34%), m. p. 84°, $[\alpha]_D$ +14°.

The production of only a *single* epimeride in each acetolysis shows that a bimolecular replacement (S_N2) proceeding with inversion of configuration is solely responsible for the substitution process, and, since the configurations of the epimeric cholestan-7-ols are established, determines the configurations of the two 7-chlorocholestanes as (I) and (III) respectively.

Secondary alkyl halides, *e.g.*, (I), (III), in non-aqueous media and in the absence of effective basic reagents give olefins, here cholest-7-ene, by the unimolecular elimination mechanism ($E1$); the absence of unimolecular acetolysis involving racemisation (S_N1), in which the slow halogen-ionisation stage would also be the initial stage of the elimination reaction ($E1$), suggests that the stability of the cholestan-7-yl cation is less than that of the cholestan-3-yl cation. Either the life of the cholestan-7-yl cation is too short to permit reaction with the weakly nucleophilic acetate anion, or the rate of reaction with the acetate anion may be so slow relatively to the internal depolarisation of the cation that co-ordination is completely excluded. The proportions of the epimeric chlorides involved in substitution and elimination appear to depend on the circumstance that steric retardation operates in bimolecular nucleophilic substitutions (S_N2) but not in unimolecular eliminations ($E1$) (Dostrovsky, Hughes, and Ingold, *J.*, 1946, 186). Since 7α-chlorocholestane (I) reacts chiefly by elimination (S_N2 15%, $E1$ 78%) whereas 7β-chlorocholestane (III) reacts mainly by substitution (S_N2 43%, $E1$ 34%), the repulsive non-bonded interactions in the S_N2 linear transition states must be greater for (I) [(1 : 2-OAc;6β-H) + (1 : 2-OAc;8β-H) + (1 : 4-OAc;10β-Me)] than for (II) [(1 : 3-OAc;5α-H) + (1 : 3-OAc;9α-H) + (1 : 3-OAc;14α-H)] (cf. Barton, *Chem. and Ind.*, 1953, 664).

An examination has been made of the relative ease with which the epimeric 7-chlorocholestanes undergo dehydrohalogenation and of the products formed. Both chlorides were stable to pyridine at 116°; 7α-chlorocholestane (I) by treatment with *s*-collidine at 170° gave some unsaturated material, but 7β-chlorocholestane (III) was recovered unchanged and unaccompanied by unsaturated products. With quinoline at 238°, 7α-chlorocholestane (I) gave a mixture of cholest-6-ene (V) (25%) and cholest-7-ene (VI) (75%), m. p. 69—71°, $[\alpha]_D$ −13°, whilst 7β-chlorocholestane (III) gave a similar mixture of cholest-6-ene (V) (20%) and cholest-7-ene (VI) (80%), m. p. 70—72°, $[\alpha]_D$ −7°.



(I) (V) (VI) (III)

M. p. 86°, $[\alpha]_D$ −88° M. p. 85°, $[\alpha]_D$ +12°

It is known from the above acetolyses that the cholestan-7-yl cation, derivable equally from either chloride, expels a proton to give cholest-7-ene unaccompanied by cholest-6-ene (example of super-Saytzew orientation); the formation of cholest-6-ene from both chlorides therefore cannot occur by a unimolecular elimination ($E1$). Since the tertiary base quinoline appears to be too weak to promote a bimolecular elimination ($E2$), it seems probable that it acts here as a thermal medium. In the case of 7α-chlorocholestane

[I; 6α-H(equatorial); 7α-Cl(axial); *cis*], thermal *cis*-elimination can afford only cholest-6-ene, whereas in the case of 7β-chlorocholestane [III; 6β- or 8β-H(axial); 7β-Cl(equatorial); *cis*] can furnish both cholest-6-ene and cholest-7-ene.

Experimental

For general experimental directions see preceding paper. $[\alpha]_D$ are in $CHCl_3$; ultra-violet absorption spectra were determined in EtOH on a Unicam SP.500 spectrophotometer with corrected scale.

Cholestan-7β-ol, m. p. 113°, was prepared from cholestan-7-one by reduction with sodium–butan-1-ol, and cholestan-7α-ol, m. p. 98°, by use of lithium aluminium hydride (Cremlyn and Shoppee, preceding paper).

7α-Chlorocholestane.—Cholestan-7β-ol (1 g.; dried at 100°/0·01 mm.) in chloroform (60 c.c.) containing dry calcium carbonate (1·3 g.) in suspension was treated with phosphorus pentachloride (2 g.; freshly sublimed) added during 45 min. at 0° with shaking. The mixture was shaken for 2 hr. at 0°, then for 1·5 hr. at 20°, set aside for 19 hr. at 20°, poured into sodium hydrogen carbonate solution containing ice, and extracted with ether. The resultant oil (1·3 g.) contained unsaturated material, and was stirred with chromium trioxide (700 mg.) in acetic acid (35 c.c.) at 60° for 0·5 hr.; after removal of acetic acid at 35°/10 mm., the mixture was poured into 2N-sodium carbonate and extracted with ether. The product (1·15 g.) gradually crystallised and was chromatographed on neutralised aluminium oxide (30 g.) in pentane. Elution with pentane (2 × 100 c.c.) furnished an oil (570 mg.) which crystallised, and by recrystallisation from acetone gave *7α-chlorocholestane* (55%), m. p. 76—78°, $[\alpha]_D$ −21° (*c*, 4·7) [Found (after drying at 60°/0·01 mm. for 10 hr.): Cl, 8·9. $C_{27}H_{47}Cl$ requires Cl, 8·7%], giving no colour with tetranitromethane–chloroform.

7α-Bromocholestane.—Cholestan-7β-ol (322 mg.) in chloroform (20 c.c.) containing dry calcium carbonate (1·1 g.) in suspension, by reaction with phosphorus pentabromide (2·2 g.; freshly sublimed) at −8° and subsequent treatment as above, gave a yellow oil, which was chromatographed on neutralised aluminium oxide (30 g.) in pentane. Elution with pentane (3 × 100 c.c.) gave an oil (180 mg.), which crystallised on cooling, and twice recrystallised from acetone gave *7α-bromocholestane*, m. p. 108—109°, $[\alpha]_D$ −20° (*c*, 3·92) [Found (after drying at 20°/0·01 mm. for 12 hr.): C, 71·6, H, 10·3. $C_{27}H_{47}Br$ requires C, 71·8; H, 10·4%].

7β-Chlorocholestane.—(*a*) Cholestan-7β-ol (1·6 g.) was treated with thionyl chloride (8 c.c.; purified by distillation over quinoline, and fractionation from a small amount of linseed oil) at 20° and the mixture refluxed for 3 hr. The product was poured on ice and worked up in the usual way, to give a brown oil which was chromatographed on neutralised aluminium oxide (45 g.) in pentane. Elution with pentane (2 × 200 c.c.) gave an oil (948 mg.), which crystallised on trituration with acetone; three recrystallisations from acetone furnished 7β-chlorocholestane (59%), m. p. 66—68°, $[\alpha]_D$ +77° (*c*, 3·5) [Found (after drying at 20°/0·01 mm. for 16 hr.): Cl, 8·75. $C_{27}H_{47}Cl$ requires Cl, 8·7%].

(*b*) Cholestan-7β-ol (270 mg.) in ether (12 c.c.) was added dropwise at 0° during 20 min. to a solution of purified thionyl chloride (10 c.c.) in ether (12 c.c.) containing dry calcium carbonate (950 mg.). The mixture was shaken at 0° for 1 hr. and left at 15° for 19 hr. The reaction product, isolated in the usual way, was chromatographed on neutralised aluminium oxide (15 g.) in pentane. Elution with pentane (2 × 30 c.c.) gave a colourless oil (42 mg.), which crystallised, and by recrystallisation from acetone yielded cholest-7-ene, m. p. and mixed m. p. 84—85°. Futher elution with pentane and benzene–pentane (1 : 1) gave oils (total 215 mg.) giving a yellow colour with tetranitromethane; after oxidation of this oil as above with chromium trioxide–acetic acid at 60° for 0·5 hr., the product (166 mg.) was chromatographed on aluminium oxide (10 g.) in pentane. Elution with pentane (2 × 50 c.c.) gave 7β-chlorocholestane (30 mg.), m. p. and mixed m. p. 64—67° after recrystallisation from acetone. Elution with benzene–pentane (1 : 4, 1 : 1) gave oils (60 mg.) which solidified and by crystallisation from acetone gave *cholestan-7β-yl sulphite*, m. p. 90—94° [Found (after drying at 15°/0·02 mm. for 17 hr.): C, 80·0; H, 11·7. $C_{54}H_{94}O_3S$ requires C, 79·0; H, 11·5%].

Acetolysis of 7α-Chlorocholestane.—7α-Chlorocholestane (310 mg.), freshly fused potassium acetate (3·5 g.), and anhydrous acetic acid (8 c.c.) were refluxed with exclusion of moisture for 30 hr. The cooled mixture was poured into 2N-sodium carbonate (30 c.c.) and extracted with ether. The product, isolated in the usual way, was hydrolysed by refluxing 4% methanolic potassium hydroxide (30 c.c.) for 3 hr. After addition of a little water, and saturation with

carbon dioxide, methanol was removed in a vacuum and the product extracted with ether. The residual oil (300 mg.) was chromatographed on neutralised aluminium oxide (18 g.) in pentane, 60-c.c. eluates being collected. Elution with pentane (fractions 1—3) gave an oil (236 mg.), which crystallised spontaneously, and by recrystallisation from acetone gave cholest-7-ene, m. p. and mixed m. p. 83°; benzene–pentane mixtures (fractions 4—11) gave only oils (total, 10·5 mg.), but use of benzene–pentane (1 : 1) (fractions 12—18) and benzene (fractions 19—22) gave material (total, 45 mg.), which crystallised when rubbed with acetone, and by recrystallisation from ether–methanol gave cholestan-7β-ol, m. p. and mixed m. p. 113°. Elution with ether–benzene (1 : 4) yielded only yellow oil (4 mg.). Total material eluted : 295 mg.

Acetolysis of 7β-*Chlorocholestane.*—7β-Chlorocholestane (370 mg.) was subjected to acetolysis under the conditions employed for the 7α-epimeride, and furnished a hydrolysed product which was chromatographed on neutralised aluminium oxide (25 g.) in pentane, 60-c.c. eluates being collected. Elution with pentane (fraction 1) gave an oil (114 mg.) which crystallised spontaneously, and by recrystallisation from acetone gave cholest-7-ene, m. p. 82—84°. Futher elution with pentane and benzene–pentane (1 : 9, 1 : 4) (fractions 2—8) gave oils (total 39 mg.) which failed to crystallise. Use of benzene–pentane (1 : 1) gave (fractions 9—12, 13—16, 17—20) crystalline material (86, 49, 12 mg.), which by combination and recrystallisation fram acetone gave cholestan-7α-ol, m. p. and mixed m. p. 96—98°. Elution with ether–benzene (1 : 3) gave only uncrystallisable oil (45 mg.). Total material eluted : 345 mg.

Action of Pyridine, s-*Collidine, and Quinoline.*—Both the epimeric 7-chlorocholestanes were stable to pyridine at 115° for 3 hr. and were recovered unchanged. 7α-Chlorocholestane (75 mg.) was refluxed with *s*-collidine (8 c.c.) for 3 hr.; the product, isolated in the usual way, was purified by filtration in pentane solution through neutralised aluminium oxide. After washing with pentane (200 c.c.), evaporation of the filtrate gave a colourless oil (72 mg.), which crystallised and by crystallisation from acetone gave unchanged 7α-chlorocholestane (55 mg.), m. p. and mixed m. p. 74—76°, giving no colour with tetranitromethane–chloroform. The mother-liquor on evaporation yielded a colourless oil (15 mg.), $[\alpha]_D$ +8° (*c*, 0·7), giving a yellow colour with tetranitromethane–chloroform. Similar treatment of 7β-chlorocholestane (75 mg.) furnished a colourless oil (69 mg.), which crystallised and by crystallisation from acetone gave 7β-chlorocholestane (59 mg.), m. p. and mixed m. p. 65—67°; the material in the mother-liquor gave no yellow colour with tetranitromethane–chloroform.

7α-Chlorocholestane (75 mg.) was refluxed with quinoline (8 c.c.) for 3 hr.; most of the quinoline was removed under reduced pressure, and the dark brown oil worked up in the usual manner. The product was dissolved in pentane and filtered through a column of neutralised aluminium oxide prepared in pentane. Elution with pentane (200 c.c.) gave a colourless oil (70 mg.), which crystallised on trituration with acetone. Recrystallisation from acetone–ether yielded plates (54 mg.), m. p. 67—69°, giving a negative Beilstein test and a yellow colour with tetranitromethane–chloroform; a second recrystallisation gave plates, m. p. 69—71°, $[\alpha]_D$ −13° (*c*, 1·72), consisting of an inseparable mixture of cholest-6-ene (25%) and -7-ene (75%). Similar treatment of 7β-chlorocholestane (80 mg.) gave a colourless oil (75 mg.), which crystallised and on recrystallisation from acetone yielded glistening plates (58 mg.), m. p. 65—70°, giving a negative Beilstein test and a yellow colour with tetranitromethane. A further recrystallisation from the same solvent furnished plates, m. p. 70—72°, $[\alpha]_D$ −7° (*c*, 2·17), consisting of an inseparable mixture of cholest-6-ene (20%) and -7-ene (80%).

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Synthetic and Stereochemical Investigations of Reduced Cyclic Bases. Part IV. The Constitutions of the Exhaustive Methylation Products of* trans-*Octahydro*-N-*methylindole and of* cis- *and* trans-*Decahydro*-N-*methyl*isoquinoline.

By F. E. King and H. Booth.

[Reprint Order No. 5316.]

The probable constitutions of the exhaustive methylation products of *trans*-octahydro-*N*-methylindole have been elicited and the investigations extended to the *cis*- and *trans*-decahydro-*N*-methyl*iso*quinolines.

The mixed bases obtained by Raney nickel reduction of *iso*quinoline with methanol as solvent, or by methylation of the secondary amines similarly prepared in *cyclo*hexane, have been separated by crystallisation of the amine picrates or of their salts with 3 : 5-dinitrobenzoic acid.

Exhaustive methylation of the *cis*- and *trans*-amines by Hofmann's method gave respectively *cis*- and *trans*-1-*NN*-dimethylaminomethyl-2-vinyl*cyclo*hexane. The methine bases were reduced to the corresponding ethyl*cyclo*hexanes and further degraded to 1-ethyl-2-methylene*cyclo*hexane.

It has been established by Barltrop, King, and Walley (*J.*, 1945, 277) that the decomposition of *cis*-octahydro-*NN*-dimethylindolinium hydroxide involves fission of the N–$C_{(8)}$ bond since the resulting methine $C_{10}H_{19}N$ yields 2-dimethylaminoethyl*cyclo*hexane as its dihydro-derivative. On the other hand, degradation of the corresponding *trans*-methohydroxide (I) produces a new methine $C_{10}H_{19}N$ and a dibasic ether $C_{20}H_{40}ON_2$, the dihydro-derivative of the unsaturated amine differing from either compound theorctically obtainable from the normal opening of the pyrrolidine ring (see King, Bovey, Mason, and Whitehead, Part III *).

Further consideration of this anomalous reaction suggests that the methine base arises from a Wagner–Meerwein type rearrangement of the carbonium ion (II) formed by ring-scission at $C_{(8)}$, thus indicating (III) as its probable structure. Data provided by *C*-methyl analysis, which was negative for the methine base but gave a value corresponding to one terminal methyl group for the dihydro-compound, are in agreement with this conclusion.

The contrasting behaviour of the *cis*- and *trans*-octahydroindole methohydroxides may be due to conformational differences in the respective molecules. In one at least of the feasible structures of the *cis*-compound (A) the necessary requirement for the normal Hofmann reaction is satisfied, *viz.*, coplanarity of the four participating centres N–C–C–H, although, because this cannot apply to the relevant centres in the pyrrolidine ring, ring scission follows a different course from that observed in the decahydroquinolines. In the *trans*-base (B), however, the necessary coplanarity does not exist and methine formation is inhibited, but by a simple electronic transition a carbonium ion is obtained which permits of molecular rearrangement by ring contraction, for example, of the kind cited by Barton (*J.*, 1953, 1032).†

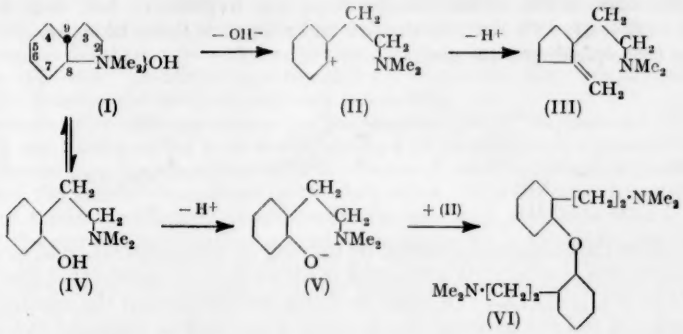
The formation of the ether $C_{20}H_{40}ON_2$ is similar to that of bimolecular products from quinolinium hydroxides (R. C. Elderfield, "Heterocyclic Compounds," J. Wiley and Sons, New York, 1952, Vol. IV, p. 232), and presumably arises from the intervention of the related alcohol (IV) by combination of the anion (V) with (II), whence its constitution is apparently (VI).

Experimental verification of these conclusions by a further study of the two amines (III) and (VI) is rendered difficult by the relative inaccessibility of *trans*-octahydroindole. The possibility that more available cyclic amines might be of use in this undertaking led to

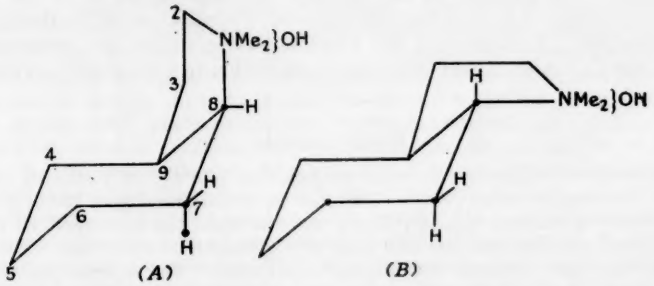
* Part III, *J.*, 1953, 250.

† This interpretation of our results was personally communicated to Dr. J. McKenna who subsequently included it in an article on the stereochemical course of Hofmann elimination in reduced cyclic amines (*Chem. and Ind.*, 1954, 406). F. E. K.

an investigation of the preparation and exhaustive methylation of *cis*- and *trans*-decahydro-*N*-methyl*iso*quinoline (VII and its geometrical isomer), which, were the methylene base (VIII) to be the primary product, would afford, *e.g.*, by oxidation to the related *cyclo*hexanone, a relatively easy route to the required products.



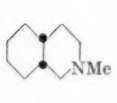
The complete hydrogenation of *iso*quinoline was described first by Skita (*Ber.*, 1924, **57**, 1977) who used colloidal platinum in acetic acid and obtained a decahydro*iso*quinoline which was probably largely the *cis*-isomer. Witkop (*J. Amer. Chem. Soc.*, 1948, **70**, 2617) found that with a platinum catalyst in acetic acid containing sulphuric acid the product consisted of approximately 70—80% of *cis*- and 20% of *trans*-decahydro*iso*quinoline which were separated by fractional crystallisation of the picrates. Hydrogenation in methyl*cyclo*hexane over Raney nickel (*idem, ibid.*, 1949, **71**, 2559) yielded a mixture containing some 80% of the *trans*-amine, the pure *trans*-base being isolated by removal of the *cis*-compound in a selective dehydrogenation process.



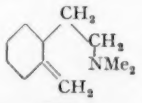
In the present investigation *iso*quinoline was hydrogenated in methanol solution over Raney nickel (W5) at 190°. At this temperature alkylation by the solvent takes place and a mixture of *cis*- and *trans*-decahydro-*N*-methyl*iso*quinoline was obtained. In contrast to Witkop's results with the secondary amines, it was not possible to secure a satisfactory separation of the mixed tertiary bases with picric acid; crystallisation, from acetone, gave less than 10% of the *trans*-amine picrate, indicating thereby a large preponderance of the *cis*-base. With 3 : 5-dinitrobenzoic acid, on the other hand, approximately 50—60% of the less-soluble *cis*-compound was obtained at the first crystallisation, the precise amount apparently depending on the batch of catalyst used. After separation of the *cis*-decahydro-*N*-methyl*iso*quinoline 3 : 5-dinitrobenzoate, the residue was worked up as the picrate, the first crystallisation yielding some 16% of the *trans*-amine salt.

Reduction in *cyclo*hexane solution at 195°, which was appreciably slower than in methanol, gave the mixed decahydro*iso*quinolines which before separation were methylated with formaldehyde–formic acid. Fractionation of the resulting tertiary amines as before,

first as 3 : 5-dinitrobenzoates and then as picrates, gave nearly equal quantities of the two isomers, but owing to losses in crystallisation the yields of crude derivatives afford only an approximate estimate of the relative quantities of the amines formed in the reduction, although it is evident that the ratio of *cis* and *trans* is diminished when *cyclo*hexane replaces methanol as solvent. Measurements on the pure *cis*- and *trans*-decahydro-*N*-methyl*iso*quinolines afford further evidence for the hypothesis (see von Auwers and Ottens, *Ber.*, 1924, **67**, 437) that the density and refractive index of *cis*-isomerides exceed those of the corresponding *trans*-compounds.



(VII)



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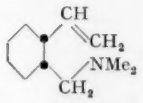
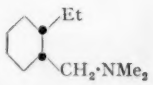
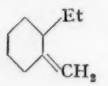


(IX)



(X)



(XI)

Distillation of the compound obtained by treating an aqueous solution of *cis*-decahydro-*N*-methyl*iso*quinoline methiodide with silver oxide yielded an unsaturated base which was presumed to be (VIII) or (IX). In order to decide its constitution the unsaturated amine was hydrogenated and the resulting dihydro-derivative likewise subjected to the Hofmann reaction. Oxidation of the hydrocarbon thus obtained gave 2-ethyl*cyclo*hexanone, thereby identifying it as 1-ethyl-2-methylene*cyclo*hexane (XI); it therefore follows that the primary exhaustive methylation product is *cis*-1-*NN*-dimethylaminomethyl-2-vinyl*cyclo*hexane (IX), its dihydro-derivative having the structure (X). Owing to decomposition by loss of methanol, distillation of the methohydroxide of (X) led to a 50% recovery of the parent amine. On the other hand, only traces of the *cis*-decahydro-*N*-methyl*iso*quinoline were regenerated during its conversion into (IX), which were easily eliminated in the crystallisation of derivatives of the methine base.

The decomposition of *trans*-decahydro-*N*-methyl*iso*quinoline methohydroxide was analogous to that of the *cis*-hydroxide in giving *trans*-1-*NN*-dimethylaminomethyl-2-vinyl*cyclo*hexane. The identity of the methine was ascertained as in the case of the corresponding *cis*-amine, *i.e.*, by reduction and further application of the Hofmann reaction to the dihydro-base. This afforded the ethylmethylene*cyclo*hexane previously obtained from the *cis*-base (X) as was again shown by its oxidation to 2-ethyl*cyclo*hexanone.

Experimental

cis-*Decahydro*-N-*methyl*isoquinoline.—(*a*) *iso*Quinoline (20 g.), in methanol (50 c.c.), was hydrogenated over Raney nickel (W5) at 190° and an initial pressure of 130 atm. After 8 hr. a further quantity of catalyst was introduced and the reduction continued for an additional 8 hr. The filtered solution was acidified with 8% hydrochloric acid, then heated to remove methanol, and non-basic material was removed with ether. The aqueous solution was made alkaline and the basic oil collected in ether. The mixed amines (21·5 g.), b. p. 85·5—89·5°/15 mm., were treated with 3 : 5-dinitrobenzoic acid (30 g.) dissolved in the minimum of boiling ethyl acetate and, on cooling, cis-*decahydro*-N-*methyl*isoquinoline 3 : 5-*dinitrobenzoate* (25 g., 49%) crystallised in square prisms, m. p. 157—162°. Further recrystallisations from ethyl acetate gave the pure salt, m. p. 165—168° (Found: C, 55·9; H, 6·5; N, 11·4. $C_{17}H_{23}O_6N_3$ requires C, 55·9; H, 6·3; N, 11·5%). Decomposition of the salt with aqueous alkali and ether-extraction gave cis-*decahydro*-N-*methyl*isoquinoline, b. p. 95·5°/24 mm. The base had b. p. (Siwoloboff) 212°/765 mm., d_4^{23} 0·910, n_D^{23} 1·4819, $[M]_R$ 48·01 (calc. 48·18), and afforded the following derivatives: picrate, crystallising from ethanol in yellow needles, m. p. 210—211° (Witkop, *loc. cit.*, records m. p. 210°) (Found: C, 50·3; H, 5·8; N, 14·8. Calc. for $C_{16}H_{22}O_7N_4$: C, 50·2; H, 5·8; N, 14·7%); *picrolonate*, crystallising from ethanol in clusters of needles, m. p. 183·5—185° (Found: C, 57·3; H, 6·5; N, 16·5. $C_{20}H_{27}O_5N_5$ requires C, 57·5; H, 6·5; N, 16·8%); *methiodide*, needles, m. p. 319° (decomp.), from ethanol (Found: C, 44·8; H, 7·5; N, 4·6; I, 43·4. $C_{11}H_{22}NI$ requires C, 44·8; H, 7·5; N, 4·7; I, 43·0%); *methopicrate*, crystallising from ethanol in prisms, m. p. 149—150° (Found: C, 51·7; H, 6·2; N, 14·1. $C_{17}H_{24}O_7N_4$ requires C, 51·5; H, 6·1; N, 14·1%).

(*b*) A solution of *iso*quinoline (20 g.) in *cyclo*hexane (50 c.c.) was hydrogenated over Raney nickel at 195° and an initial pressure of 130 atm. for 20 hr., fresh catalyst being introduced after 10 hr. The mixed decahydro*iso*quinolines were extracted from the filtered solution with 8% hydrochloric acid and when liberated with alkali were isolated with ether and heated with 40% aqueous formaldehyde (20 c.c.) and 90% formic acid (35 c.c.) under reflux for 12 hours. The oily tertiary amines (21·5 g.) were isolated by extraction of the basified solution with ether and treated with 3 : 5-dinitrobenzoic acid (30 g.); the resulting salt was crystallised from ethyl acetate, giving *cis*-decahydro-*N*-methyl*iso*quinoline 3 : 5-dinitrobenzoate (10·9 g.) as square prisms, m. p. 156—160°. A further quantity (1·7 g.), m. p. 143—149°, was isolated from the mother-liquors, bringing the total yield of crude salt to 25%.

trans-*Decahydro*-N-*methyl*iso*quinoline*.—(*a*) *iso*Quinoline (20 g.), in methanol (50 c.c.), was hydrogenated over Raney nickel as in the preparation of *cis*-decahydro-*N*-methyl*iso*quinoline. The mother-liquors from the crystallisation of the *cis*-base 3 : 5-dinitrobenzoate were evaporated to dryness and the residue decomposed with dilute alkali. The liberated base (10·3 g.) was recovered by extraction into ether. Treatment of the base with picric acid (15·5 g.) and crystallisation of the picrate from acetone yielded *trans*-decahydro-*N*-methyl*iso*quinoline picrate (7·4 g.), m. p. 227—229°. A further quantity (1·3 g., total yield 16%), having m. p. 224—226°, was recovered from the mother-liquors. Further recrystallisations from acetone gave the pure *trans*-picrate, m. p. 237° (decomp.) (Witkop, *loc. cit.*, records 237°) (Found: C, 50·4; H, 5·7; N, 14·9%). Decomposition of the picrate with lithium hydroxide yielded trans-*decahydro*-N-*methyliso*quinoline, b. p. 104°/40 mm. The base had b. p. (Siwoloboff) 209·5°/752 mm., d_4^{20} 0·893, n_D^{20} 1·4756, $[M]_R$ 48·4 (calc., 48·18), and afforded the following derivatives: picrolonate, crystallising from ethanol in square prisms, m. p. 221—222° [Witkop, *J. Amer. Chem. Soc.*, 1949, **71**, 2559, records m. p. 216—219° (sinters at 198°)] (Found: C, 57·7; H, 6·2; N, 17·0%); *methiodide*, needles, m. p. 283—284°, from ethanol (Found: C, 44·9; H, 7·5; N, 4·4; I, 43·3%); *methopicrate*, crystallising from water in yellow needles, m. p. 108—109° (Found: C, 51·2; H, 6·4; N, 14·2%); *mono*-3 : 5-*dinitrobenzoate*, which crystallised from ethyl acetate in needles, m. p. 146—148·5° (Found: C, 55·9; H, 6·0; N, 11·5%); *bis*-3 : 5-*dinitrobenzoate*, prepared as prisms, m. p. 115—117·5°, by mixing ethereal solutions of the two components (Found: C, 50·3; H, 4·7; N, 12·3. $C_{24}H_{27}O_{12}N_5$ requires C, 49·9; H, 4·7; N, 12·1%).

(*b*) *iso*Quinoline (20 g.), in *cyclo*hexane (50 c.c.), was hydrogenated over Raney nickel as in the preparation of *cis*-decahydro-*N*-methyl*iso*quinoline. The filtrates from the crystallisation of the *cis*-base 3 : 5-dinitrobenzoate were evaporated to dryness and the residue was decomposed with dilute alkali to give the free base (13·5 g.) which was recovered by ether-extraction. Treatment of the base with picric acid (20·2 g.) and crystallisation from acetone gave *trans*-decahydro-*N*-methyl*iso*quinoline picrate (11·4 g.), m. p. 231—233°. A further quantity (4·0 g., total yield 29%), m. p. 222—224°, was recovered from the mother-liquors.

Exhaustive Methylation of cis-*Decahydro*-N-*methyl*iso*quinoline*.—A solution of the *cis*-decahydro-*N*-methyl*iso*quinoline methiodide (21·7 g.) in water (300 c.c.) was shaken in the dark with silver oxide, freshly prepared from silver nitrate (24 g.) and sodium hydroxide (7 g.). When a sample of the filtered solution gave a negative iodide test (*ca.* 5 hr.), the mixture was filtered and the filtrate evaporated under reduced pressure at 45—50°. After most of the water had been removed, the temperature was raised to 120—130°; the syrupy quaternary hydroxide yielded a distillate of cis-1-NN-*dimethylaminomethyl*-2-*vinyl*cyclo*hexane* (IX) (9·9 g., 81%), b. p. 108—109° 46 mm. The base gave the following derivatives: *picrate*, crystallising from ethanol in prisms, m. p. 111—113° (Found: C, 51·4; H, 5·8; N, 14·2. $C_{17}H_{24}O_7N_4$ requires C, 51·5; H, 6·1; N, 14·1%); *methiodide*, crystallising in plates, m. p. 253—254°, from acetone or acetone–ethyl acetate (Found: C, 46·5; H, 7·5; N, 4·2; I, 41·5. $C_{13}H_{24}NI$ requires C, 46·6; H, 7·8; N, 4·5; I, 41·0%); *methopicrate*, prisms, m. p. 139—140°, from ethanol (Found: C, 53·1; H, 6·2; N, 13·7. $C_{18}H_{26}O_7N_4$ requires C, 52·7; H, 6·4; N, 13·7%). When the methiodide (9·6 g.) of the crude base was dissolved in cold acetone (150 c.c.) a residue of *cis*-decahydro-*N*-methyl*iso*quinoline methiodide (0·12 g.), m. p. 306—307°, was obtained.

A sample of *cis*-1-NN-dimethylaminomethyl-2-vinyl*cyclo*hexane purified through the picrate had b. p. (Siwoloboff) 210°/763 mm., n_D^{20} 1·4679.

cis-1-NN-*Dimethylaminomethyl*-2-*ethyl*cyclo*hexane* (X).—The unsaturated base (IX) (10·3 g.) was hydrogenated in the form of its hydrochloride in methanol (100 c.c.) over palladised charcoal at room temperature and pressure. After filtration, the solution was evaporated and the residue treated with aqueous alkali and extracted with ether. cis-1-NN-*Dimethylaminomethyl*-2-*ethyl*-cyclo*hexane* (10 g., 96%) was thus isolated as an oil, b. p. 93·5°/24 mm., which yielded the following derivatives: *picrate*, crystallising from ethanol in prisms, m. p. 105—107° (Found: C,

51·6; H, 6·8; N, 14·2. $C_{17}H_{26}O_7N_4$ requires C, 51·3; H, 6·6; N, 14·1%); *methiodide*, plates, m. p. 278—279°, from acetone (Found: C, 46·4; H, 8·0; N, 4·2; I, 41·2. $C_{12}H_{26}NI$ requires C, 46·3; H, 8·4; N, 4·5; I, 40·8%); *methopicrate*, crystallising from ethanol in prisms, m. p. 145—146° (Found: C, 52·7; H, 6·7; N, 13·4. $C_{18}H_{28}O_7N_4$ requires C, 52·4; H, 6·8; N, 13·6%). A sample of the base purified through the picrate had b. p. (Siwoloboff) 208°/759 mm., n_D^{19} 1·4595.

1-*Ethyl*-2-*methylene*cyclo*hexane* (XI).—A solution of the methiodide (6·15 g.) in water (150 c.c.) was shaken with silver oxide freshly prepared from silver nitrate (8 g.). The filtered solution was evaporated at 45—50° and the syrupy residue heated under reduced pressure at 120°. An oil (0·9 g.) isolated by ether-extraction of the distillate was resolved with dilute hydrochloric acid into a neutral and a basic fraction, the latter (0·4 g.) being identified as *cis*-1-*NN*-dimethylaminomethyl-2-ethyl*cyclo*hexane (IX) by mixed m. p. of the picrate, m. p. 105—107°, and methiodide, m. p. 280°. The neutral fraction (0·45 g.) consisting of 1-ethyl-2-methylene-*cyclo*hexane, had b. p. (Siwoloboff) 152—153°/766 mm., n_{19}^{D} 1·4581. The olefin (0·35 g.) was dissolved in acetone (100 c.c.) and potassium permanganate (1 g.) was added at intervals during 2 days. Finally, after refluxing for 10 min. the solution was filtered from manganese dioxide and evaporated. The oily residue (0·2 g.) gave 2-ethyl*cyclo*hexanone 2 : 4-dinitrophenylhydrazone, crystallising from alcohol in red needles, m. p. 162·5—163·5° (Found: N, 18·1. Calc. for $C_{14}H_{18}O_4N_4$: N, 18·3%). An authentic specimen had m. p. 161·5—162° (cf. King, Barltrop, and Walley, *J.*, 1945, 279) and the mixed m. p. was 162—162·5°.

Exhaustive Methylation of trans-*Decahydro*-N-*methyl*iso*quinoline*.—This was carried out as already described for the *cis*-isomer. The *trans*-methiodide (6·5 g.) yielded *trans*-1-*NN*-dimethylaminomethyl-2-vinyl*cyclo*hexane (3·0 g., 81%). The base gave the following derivatives: *picrate*, crystallising from ethanol in prisms, m. p. 101—102° (85—97° when mixed with the *cis*-isomer) (Found: C, 51·4; H, 6·3; N, 14·4%); *methiodide*, plates, m. p. 212°, from acetone–ethyl acetate (Found: C, 46·2; H, 7·8; N, 4·2; I, 41·1%); *methopicrate*, crystallising in prisms, m. p. 113—115°, from ethanol (Found: C, 52·5; H, 6·5; N, 13·8%).

trans-1-NN-*Dimethylaminomethyl*-2-*ethyl*cyclo*hexane* (VI).—The unsaturated *trans*-base (5·45 g.) gave, on hydrogenation over palladium–charcoal, *trans*-1-*NN*-dimethylaminomethyl-2-ethyl*cyclo*hexane (4·8 g., 87%). The base yielded a *picrate*, crystallising from ethanol in plates, m. p. 111—112° (94—103° if mixed with the *cis*-isomer) (Found: C, 50·9; H, 6·5; N, 14·1%), a *methiodide*, needles (from ethanol), m. p. 261° (decomp.) (Found: C, 46·5; H, 8·1; N, 4·2; I, 41·0%), and *methopicrate*, plates (from ethanol), m. p. 116·5—118° (Found: C, 52·1; H, 6·5; N, 13·4%).

The decomposition of *trans*-1-*NN*-dimethylaminomethyl-2-ethyl*cyclo*hexane methiodide (7·0 g.) was carried out as described for the *cis*-compound. From the distillate 1-ethyl-2-methylene-*cyclo*hexane (0·65 g.) was obtained and *trans*-1-*NN*-dimethylaminomethyl-2-ethyl*cyclo*hexane (0·27 g.) was recovered. Oxidation of the hydrocarbon gave 2-ethyl*cyclo*hexanone of which the 2 : 4-dinitrophenylhydrazone had m. p. and mixed m. p. 162—163°.

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*The Ionization of Organic Halides in Nitroalkanes. Part V.**

By Alwyn G. Evans, J. A. G. Jones, and G. O. Osborne.

[Reprint Order No. 5343.]

We have studied the effect of *ortho*- and *meta*-substitution on the thermodynamics of the ionization equilibrium of triphenylmethyl chloride in nitromethane. This equilibrium, which is of the type $RCl \rightleftharpoons R^+Cl^-$, was examined by a spectrophotometric method.

In our earlier papers, we have studied the ionization of *para*-substituted triphenylmethyl chlorides in nitroalkanes by a spectrophotometric method (Bentley, A. G. Evans, and Halpern, *Trans. Faraday Soc.*, 1951, **47**, 711; Bentley and A. G. Evans, *J.*, 1952, 3468; A. G. Evans, Jones, and Osborne, *Trans. Faraday Soc.*, 1954, **50**, 16, 470). This study is now extended to *ortho*- and *meta*-methyl, -chloro-, and -bromo-substituted triphenylmethyl chlorides.

Experimental

Materials.—The nitromethane, sulphuric acid, substituted triarylmethyl alcohols, and substituted triarylmethyl chlorides were obtained as described previously (A. G. Evans, Jones, and Osborne, *locc. cit.*). Two of the alcohols not previously described had the following characteristics: *2-chloro-4′ : 4″-dimethyltriphenylmethanol*, m. p. 98—99° (Found: C, 77·9; H, 6·3; Cl, 11·3. $C_{21}H_{19}OCl$ requires C, 78·1; H, 5·9; Cl, 11·0%); *2 : 4′ : 4″-trimethyltriphenylmethanol*, m. p. 88° (Found: C, 87·1; H, 7·34. $C_{22}H_{22}O$ requires C, 87·4; H, 7·3%). Two of the chlorides not previously prepared had the following characteristics: *2-chloro-4′ : 4″-dimethyltriphenylmethyl chloride*, m. p. 128—129° (Found: hydrolysable chlorine, 10·2. $C_{21}H_{18}Cl_2$ requires Cl^-, 10·4%); *2 : 4′ : 4″-trimethyltriphenylmethyl chloride*, m. p. 111° (Found: hydrolysable chlorine, 11·5. $C_{22}H_{21}Cl$ requires Cl^-, 11·1%).

Results

Spectra.—The spectra are shown in Figs. 1 and 2. All the alcohols except 2 : 5-dimethyl- and 2 : 4′ : 4″-trimethyl-triphenylmethanol were examined in 98% sulphuric acid in which solvent we assume that they are completely ionized. Evidence that this assumption is justified is quoted in Part IV (*loc. cit.*). 2 : 5-Dimethyl- and 2 : 4′ : 4″-trimethyl-triphenylmethanol appeared to undergo sulphonation in 98% sulphuric acid, so their spectra were measured in 85% sulphuric acid in which solution they are stable. Gold and Hawes (*J.*, 1951, 2102) have demonstrated that triphenylmethanol is fully ionized in 60% sulphuric acid, so we are justified in assuming that these alcohols are completely ionized in 85% sulphuric acid. The very close similarity seen in Figs. 1 and 2 between the spectrum of RCl in nitromethane and that of the corresponding ROH in sulphuric acid establishes the presence of the R^+ ion in the nitromethane solutions.

Nature of Equilibrium.—In Fig. 3 we plot $(D_\lambda)_{max.}$ against the concentration of un-ionized RCl. These lines are straight, demonstrating that the equilibrium is of the type

$$RCl \rightleftharpoons R^+Cl^- \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

in which the ion pairs are not dissociated. The values of the equilibrium constant, K, and of the free-energy change, ΔG° ($= -RT \ln K$), for reaction (1) have been obtained as described in Part IV, and the values of ΔG° are considered to be accurate to within $\pm 0{\cdot}1$ kcal./mole. (Again, the two methods of obtaining the R^+-ion concentration give the same ΔG° value to within $\pm 0{\cdot}1$ kcal./mole.)

Change of K *with Temperature.*—The plots of $\log_{10} D$ against $1/T$ are shown in Fig. 4. The expansion of the solvent with temperature has been allowed for in these plots. Values of ΔH° calculated from the slopes of these lines are given in Table 1. (For 2-chlorotriphenylmethyl chloride, for example, the change of optical density with temperature was determined for six solutions of different concentrations, these concentrations varying over a 2½-fold range.) For all chlorides studied, ΔH° was reproducible to within $\pm 0{\cdot}2$ kcal./mole.

* Part IV, *Trans. Faraday Soc.*, 1954, **50**, 470.

TABLE 1.

Substituents	Thermodynamic constants for ionization of substituted triphenylmethyl chlorides in nitromethane: 10^4K (T°c)	$\Delta G°$ (T°c), kcal./mole	$\Delta H°$, kcal./mole	$\Delta S°$, cal./deg.-mole	$\Delta G^{\ddagger}$ for alcoholysis of substituted diphenylmethyl chlorides, $\Delta G^{\ddagger}$, kcal./mole
Unsubstituted	4·4 (20·0°) [a]	4·5 (20·0°) [a]	1·4 [a]	−10·5 (20·0°) [a]	21·0 [d]
2-Methyl	18 (20·0°)	3·7 (20·0°)	1·6	−7·2 (20·0°)	20·2 [d]
3-Methyl	8·6 (19·0°)	4·1 (19·0°)	1·4	−9·2 (19·0°)	20·6 [d]
4-Methyl	20 (19·0°) [b]	3·6 (19·0°) [b]	1·4 [b]	−7·6 (19·0°) [b]	19·3 [d]
2 : 5-Dimethyl.....	49 (20·0°)	3·1 (20·0°)	1·7	−4·8 (20·0°)	—
2 : 4′ : 4″-Trimethyl	910 (20·0°)	1·4 (20·0°)	0·7	−2·4 (20·0°)	—
4 : 4′ : 4″-Trimethyl	540 (20·0°) [b]	1·7 (20·0°) [b]	−0·2 [b]	−6·4 (20·0°) [b]	—
2-Chloro	1·8 (21·0°)	5·0 (21·0°)	2·5	−8·5 (21·0°)	23·8 [d]
4-Chloro	1·9 (21·5°) [c]	5·0 (21·5°) [c]	1·7 [c]	−11·2 (21·5°) [c]	21·5 [d]
2-Chloro-4′ : 4″-dimethyl	81 (18·0°)	2·8 (18·0°)	0·8	−6·9 (18·0°)	—
4-Chloro-4′ : 4″-dimethyl	46·8 (18·0°) [c]	3·1 (18·0°) [c]	0·2 [c]	−10·0 (18·0°) [c]	—
2-Bromo	3·1 (18·0°)	4·7 (18·0°)	2·1	−8·9 (18·0°)	—
4-Bromo	1·9 (21·5°) [c]	5·0 (21·5°) [c]	1·6 [c]	−11·5 (21·5°) [c]	—

[a] Bentley, A. G. Evans, and Halpern, *Trans. Faraday Soc.*, 1951, **47**, 711. [b] A. G. Evans, Jones, and Osborne, *ibid.*, 1954, **50**, 16. [c] *Idem, ibid.*, p. 470. [d] Calculated from results of Norris and Banta (*J. Amer. Chem. Soc.*, 1928, **50**, 1804).

FIG. 1.

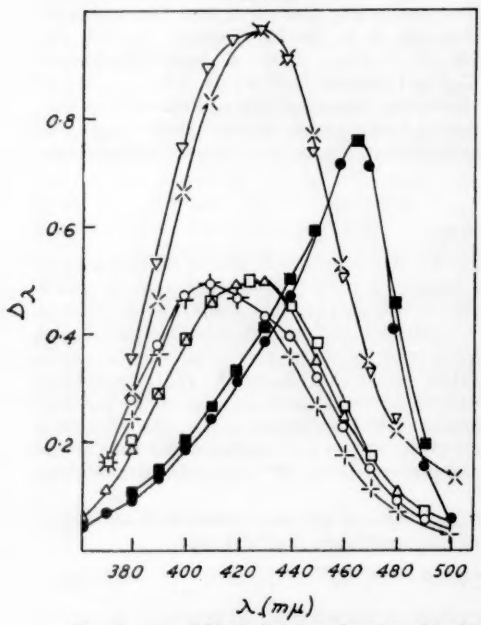


FIG. 2.

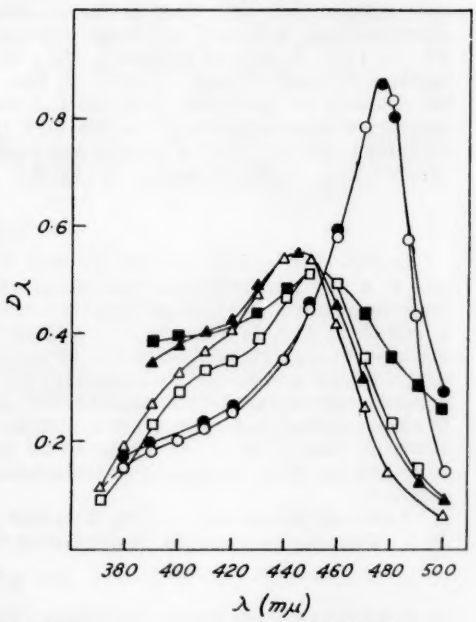


FIG. 1. △	2-Methyltriphenylmethanol in 98% H_2SO_4	1·49 × 10^{-5} mole/l.
□	2-Methyltriphenylmethyl chloride in $MeNO_2$	9·1 × 10^{-3} mole/l.
+	3-Methyltriphenylmethanol in 98% H_2SO_4	1·53 × 10^{-5} mole/l.
○	3-Methyltriphenylmethyl chloride in $MeNO_2$	1·80 × 10^{-2} mole/l.
×	2 : 5-Dimethyltriphenylmethanol in 85% H_2SO_4	2·98 × 10^{-5} mole/l.
▽	2 : 5-Dimethyltriphenylmethyl chloride in $MeNO_2$	5·87 × 10^{-3} mole/l.
●	2 : 4′ : 4″-Trimethyltriphenylmethanol in 85% H_2SO_4	1·48 × 10^{-5} mole/l.
■	2 : 4′ : 4″-Trimethyltriphenylmethyl chloride in $MeNO_2$	1·50 × 10^{-5} mole/l.
FIG. 2. △	2-Chlorotriphenylmethanol in 98% H_2SO_4	1·50 × 10^{-5} mole/l.
▲	2-Chlorotriphenylmethyl chloride in $MeNO_2$	1·00 × 10^{-1} mole/l.
□	2-Bromotriphenylmethanol in 98% H_2SO_4	1·49 × 10^{-5} mole/l.
■	2-Bromotriphenylmethyl chloride in $MeNO_2$	4·90 × 10^{-2} mole/l.
○	2-Chloro-4′ : 4″-dimethyltriphenylmethanol in 98% H_2SO_4	1·50 × 10^{-5} mole/l.
●	2-Chloro-4′ : 4″-dimethyltriphenylmethyl chloride in $MeNO_2$	1·85 × 10^{-3} mole/l.

TABLE 2. *Maximum extinction coefficients of substituted triphenylmethyl chlorides.*

Substituents	$10^{-4}\varepsilon_{max.}$	λ, mμ	Substituents	$10^{-4}\varepsilon_{max.}$	λ, mμ
Unsubstituted	3·8	430	4-Chloro	4·9	442
2-Methyl	3·4	425	2-Bromo	3·5	452
4-Methyl	4·6	446	4-Bromo	5·1	450
2 : 2′ : 2″-Trimethyl *	2·5	460	4 : 4′-Dimethyl	5·6	452
4 : 4′ : 4″-Trimethyl	7·8	450	2-Chloro-4′ : 4″-dimethyl	5·8	476
2-Chloro	3·7	444	4-Chloro-4′ : 4″-dimethyl	7·8	455

* Newman and Deno (*J. Amer. Chem. Soc.*, 1951, **73**, 3645).

FIG. 3.

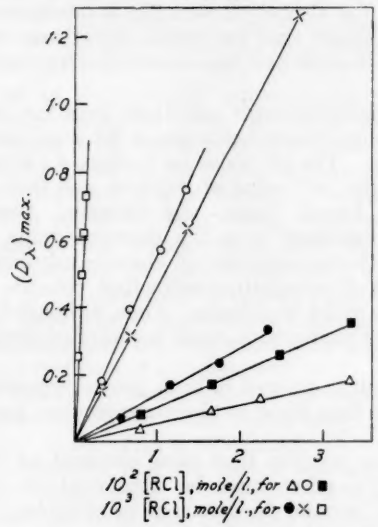


FIG. 4.

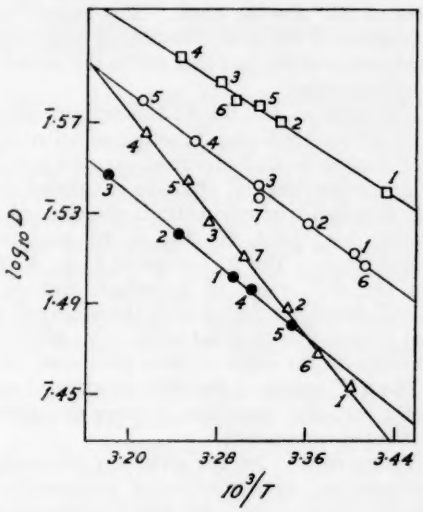


FIG. 3.

○ 2-Methyltriphenylmethyl chloride in $MeNO_2$ at 18°.
● 2 : 5-Dimethyltriphenylmethyl chloride in $MeNO_2$ at 18°.
□ 2 : 4′ : 4″-Trimethyltriphenylmethyl chloride in $MeNO_2$ at 19°.
△ 2-Chlorotriphenylmethyl chloride in $MeNO_2$ at 19°.
■ 2-Bromotriphenylmethyl chloride in $MeNO_2$ at 18°.
× 2-Chloro-4′ : 4″-dimethyltriphenylmethyl chloride in $MeNO_2$ at 18°.

FIG. 4.

○ 2-Methyltriphenylmethyl chloride.
□ 3-Methyltriphenylmethyl chloride.
● 2 : 5-Dimethyltriphenylmethyl chloride.
△ 2-Chlorotriphenylmethyl chloride.

DISCUSSION

Spectra.—From the values given in Table 2, which we obtain for the maximum extinction coefficients, ε, we see that the introduction of *para*-substituents increases the extinction coefficient of the triphenylmethyl ion, but changing the substituent from the *para*- to the *ortho*-position causes a marked decrease in the extinction coefficient, reducing it to a value similar to or even less than that of the unsubstituted ion. This effect in the 2 : 2′ : 2″-tritolylmethyl ion has been attributed by Newman and Deno (*loc. cit.*, 1951, **73**, 3645) to steric inhibition of resonance by the *ortho*-group, an effect which does not operate in the *para*-substituted ion.

Effect of Substituent Groups.—From Table 1 we see that the effects of 2-methyl, 2-chloro-, and 2-bromo-substituents upon ΔG° for the ionization are similar (to within

0·3 kcal./mole) to the effects obtained when the corresponding groups are introduced into the 4-position. We have calculated the values of $\Delta G^{\ddagger}$, the free energy of activation for the alcoholysis of substituted diphenylmethyl chlorides, from the velocity constants obtained by Norris and Banta (*J. Amer. Chem. Soc.*, 1928, **50**, 1804), and these values are given in Table 1. It is seen that for the introduction of *ortho*- and *para*-chloro-groups, the change in $\Delta G^{\ddagger}$ is in the same direction as is the corresponding change in ΔG°. The chlorine atom, however, produces a greater increase in $\Delta G^{\ddagger}$ (*i.e.*, a more marked slowing down of the reaction rate) when introduced into the *ortho*- than into the *para*-position although the corresponding effects on ΔG° are the same. In the same way, the methyl group appears to produce a smaller decrease in $\Delta G^{\ddagger}$ (*i.e.*, a less marked speeding up of the reaction) when introduced into the *ortho*- than into the *para*-position, although again the corresponding effects on ΔG° are the same. This means that if the alcoholysis were S_N1 in mechanism, the reaction of the *ortho*-substituted compound is slower than one would expect from the consideration of the fact that ΔG° is the same for both *ortho*- and *para*-substituted triphenylmethyl chlorides.

The value of ΔG° for 2 : 5-dimethyltriphenylmethyl chloride calculated from the ΔG° values of 2-methyl- and 3-methyl-substituted triphenylmethyl chlorides is 3·3 kcal./mole, which is close to that observed, *viz.*, 3·1 kcal./mole. The ΔG° value for 2-chloro-4′ : 4″-dimethyltriphenylmethyl chloride calculated from the ΔG° value of 2-chloro- and that of 4 : 4′-dimethyl-triphenylmethyl chloride (A. G. Evans, Jones, and Osborne, *Trans. Faraday Soc.*, 1954, **50**, 16), is 3·1 kcal./mole compared with the observed value of 2·8 kcal./mole. The ΔG° value of 2 : 4′ : 4″-trimethyltriphenylmethyl chloride calculated from the ΔG° value of 2-methyl- and of 4 : 4′-dimethyl-triphenylmethyl chloride is 1·8 kcal./mole, compared with the observed value of 1·4 kcal./mole. Thus, although the effect of *ortho*-groups is not so strictly additive as for *para*-groups, a fair degree of additivity still holds for the effect of these groups on ΔG°.

The ΔH° values of the *ortho*-substituted compounds are seen to be in general somewhat greater (*i.e.*, the ionization is more endothermic) than those of the corresponding *para*-substituted compounds.

Values of ΔS° for the *ortho*- are somewhat less negative than those obtained for the corresponding *para*-substituted compounds. This effect may be attributed to the intrusion of the *ortho*-group into the solvation shell around the carbon atom which has the formal positive charge, thus reducing the extent to which the solvent is " frozen " around the ion. Such a reduction in the extent to which the solvent interacts with the ion may account for the higher endothermicity of ionization of the *ortho*-compounds.

The introduction of a *meta*-methyl group into triphenylmethyl chloride causes a slight increase in ionization, as shown by the small decrease of 0·4 kcal./mole in ΔG° (compared with the decrease of 0·8 kcal./mole for the introduction of an *ortho*-methyl group). This introduction of a *meta*-methyl group involves practically no change in ΔH° or ΔS°. Lichtin and Bartlett (*J. Amer. Chem. Soc.*, 1951, **73**, 5530) have also obtained a ΔG° change of 0·4 kcal./mole for this effect in their conductimetric study of substituted triphenylmethyl chlorides in liquid sulphur dioxide. This decrease in ΔG° is paralleled by a decrease of 0·45 kcal./mole in the free energy of alcoholysis, $\Delta G^{\ddagger}$, which occurs when a *meta*-methyl group is introduced into diphenylmethyl chloride (Table 1). This parallelism has been found in Parts III and IV (*locc. cit.*) for *para*-substituent groups.

We thank the D.S.I.R. for the award of Maintenance Allowances to two of us (J. A. G. J. and G. O. O.).

UNIVERSITY COLLEGE, CARDIFF. [*Received, April 30th*, 1954.]

Infra-red Spectra of Natural Products. Part II. Compounds containing the* cyclo*Propane Ring.*

By A. R. H. Cole.

[Reprint Order No. 5351.]

The infra-red spectra of a number of steroid and terpenoid compounds containing the *cyclo*propane ring have been measured. The C–H stretching absorption at 3040—3058 cm.$^{-1}$, found when the three-membered ring contains a CH_2 group, confirms that the C–H bonds of the ring are very similar to the sp^2 type in ethylene. This information is useful in the identification of *cyclo*propane rings in unknown compounds.

Some of the chemical properties of *cyclo*propane show that it resembles unsaturated compounds rather than the larger saturated rings. For instance, it gives addition products with bromine (1 : 3-dibromopropane) and with hydrogen bromide (*n*-propyl bromide) whereas the larger-ring homologues give substitution products if they react at all. Therefore it is probable that in electronic structure a *cyclo*propane ring is somewhat similar to the ethylenic double bond, and this is reflected in its spectroscopic properties. Walsh (*Trans. Faraday Soc.*, 1949, **45**, 179) has summarised the results of ultra-violet measurements on *cyclo*propane itself and on compounds in which the three-membered ring is " conjugated " with an ethylenic double bond or a carbonyl group. In all these the absorption is more intense and at a longer wave-length than might be expected, indicating that the ring has a system of weakly bound electrons similar in behaviour to the π electrons of ethylene.

Structural Considerations.—Electron-diffraction measurements on *cyclo*propane (Bastiansen and Hassel, *Tids. Kjemi Berg. Met.*, 1946, **6**, 71) show that the H–C–H angle is 118·2° ± 2°. This is significant, since it is almost the same as that found in ethylene, and indicates that the carbon valencies towards hydrogen are close to the sp^2 hybrid type characteristic of ethylenic carbon atoms. Theoretical arguments supporting this hypothesis have been advanced by Coulson and Moffit (*Phil. Mag.*, 1949, **40**, 1) and by Walsh (*loc. cit.*). These theoretical studies also indicate that the electrons binding the carbon atoms together behave in certain ways like the electrons in the C=C bond of ethylene.

Infra-red Spectra.—In the infra-red spectrum there are two regions in which information may be obtained about the properties of the *cyclo*propane ring. First, the conjugating effect of the three-membered ring with a carbonyl group, which results in a lowering of carbonyl frequency, has been observed by Josien and Fuson (*Compt. rend.*, 1950, **231**, 1511) for 3 : 5-*cyclo*cholestan-6-one (I; C=O frequency 1690 cm.$^{-1}$) and by Jones, Humphries, Herling, and Dobriner (*J. Amer. Chem. Soc.*, 1952, **74**, 2821) for a 16 : 17-methylene-20-ketosteroid (II; C=O frequency 1685 cm.$^{-1}$).

Secondly, the region of C–H stretching absorption should show whether the C–H bonds of the *cyclo*propane ring are of the sp^2 hybrid type or not, since it is known that ethylenic C–H bonds have a considerably higher vibration frequency than have the tetrahedral type (Fox and Martin, *Proc. Roy. Soc.*, 1940, *A*, **175**, 208). It is with this region that this paper is mostly concerned. A preliminary account of this work (Cole, *Chem. and Ind.*, 1953, 946) has already been published.

Josien (*Compt. rend.*, 1950, **231**, 131) reported that in the infra-red spectra of a series of 3 : 5-*cyclo*steroids, a " point of inflexion " was observed at 3·30 μ (3030 cm.$^{-1}$), and it was suggested that this unresolved band was related to a vibration of a CH-group adjacent to the *cyclo*propane ring. Those measurements were carried out by using a lithium fluoride prism which is capable of high resolving power, and in view of the results reported below it is surprising that the band was not more completely resolved from the rest of the C–H absorption.

* Part I, *J.*, 1952, 4969.

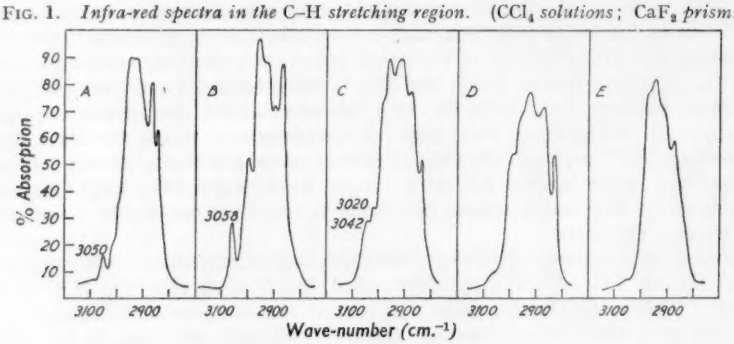
Experimental

The infra-red spectra were measured on a Grubb-Parsons spectrometer, Model S3A, equipped with a Perkin-Elmer thermocouple, chopper and rectifier assembly, and No. 81 amplifier. Prisms of calcium fluoride (3—8 μ) and sodium chloride (8—14 μ) were employed, the latter in the double-pass system which has been previously described (Cole, *J. Opt. Soc. Amer.*, 1953, **43**, 807). The compounds were studied in carbon tetrachloride for the region 3—8 μ and in carbon disulphide for 8—14 μ, and cells of 1·3 mm. and 3 mm. were employed.

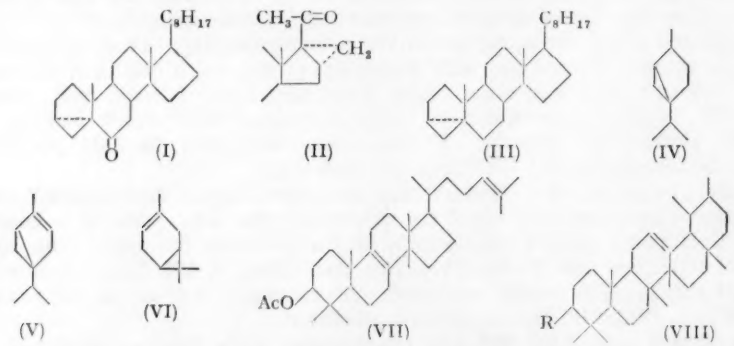
Results and Discussion

The C–H stretching region of the spectra of 3 : 5-*cyclo*cholestane (*i*-cholestane; III; *A*), thujane (IV; *B*), α-thujene (V; *C*), car-3-ene (VI; *D*) and lanosta-8 : 24-dienyl acetate (VII; *E*) * are shown in Fig. 1. The first three of these compounds have a CH_2 group included in the *cyclo*propane ring, the fourth is substituted at all carbons of the three-membered ring, and the last has no *cyclo*propane ring. It will be noticed that the band at 3024—3058 cm.$^{-1}$ only appears when there is a CH_2 group included in the *cyclo*propane ring,

Fig. 1. *Infra-red spectra in the* C–H *stretching region.* (CCl_4 *solutions*; CaF_2 *prism.*)



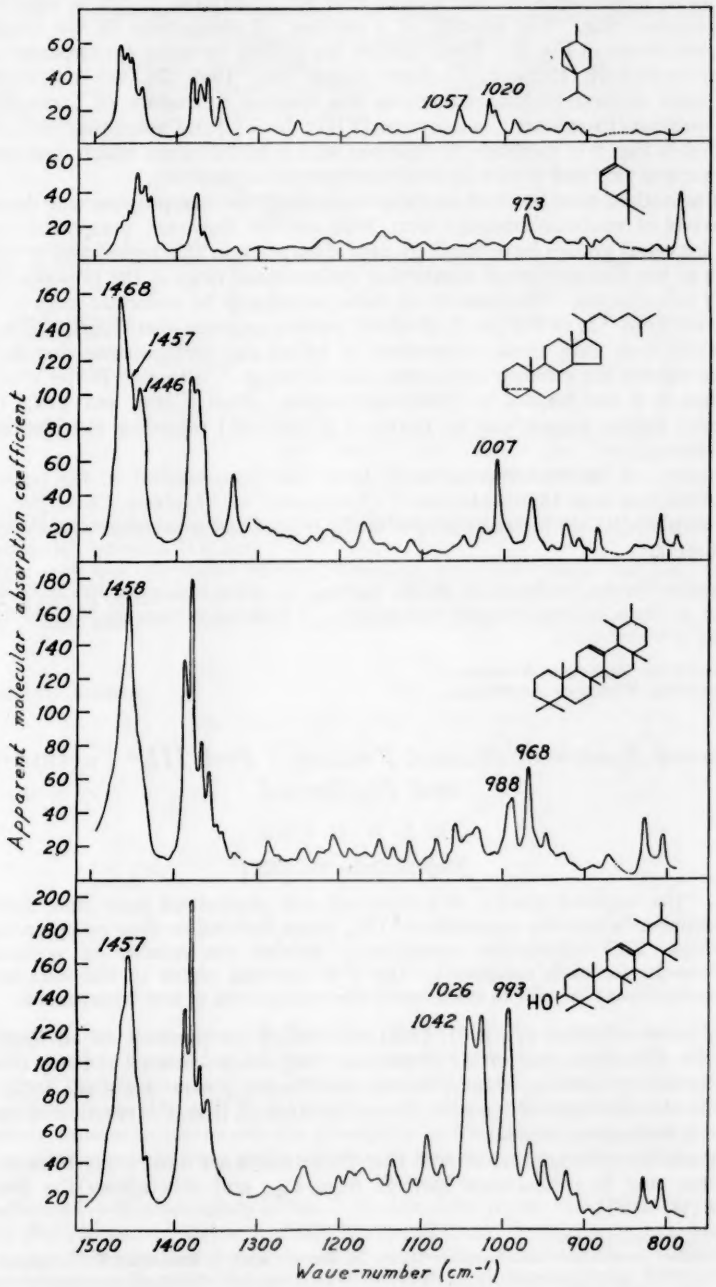
and must be due to a vibration of this particular CH_2 group. The high frequency of this absorption confirms the earlier suggestion from ultra-violet and electron-diffraction results that these C–H bonds are of sp^2 type.



CH groups attached to double bonds in steroids and similar compounds have stretching vibrations in the range 3015—3075 cm.$^{-1}$ (Jones, Williams, Whalen, and Dobriner, *J. Amer. Chem. Soc.*, 1948, **70**, 2024; Jones, Humphries, Packard, and Dobriner, *J. Amer. Chem. Soc.*, 1950, **72**, 86; Bladon, Fabian, Henbest, Koch, and Wood, *J.*, 1951, 2402). Some of the spectra in Fig. 1 exhibit this absorption, *e.g.*, α-thujene at 3020 cm.$^{-1}$, but this should not be confused with the more pronounced absorption at a higher frequency due to the

* Numbered according to standard steroid rules.

FIG. 2. *Infra-red spectra in the range* 750—1500 *cm.*$^{-1}$. *The dotted region near* 850 *cm.*$^{-1}$ *is uncertain because of* CS_2 *absorption. The slight break in the curves between* 1300 *and* 1350 *cm.*$^{-1}$ *indicates the change from* CCl_4 *solvent–*CaF_2 *prism to* CS_2 *solvent–*NaCl *prism.*



CH_2 group of the *cyclo*propane ring. The latter should be helpful in the identification of three-membered rings in certain types of unknown compounds.

Measurements at Longer Wave-lengths.—Derfer, Pickett, and Boord (*J. Amer. Chem. Soc.*, 1949, **71**, 2482) have suggested that a band near 9·9 μ (1010 cm.$^{-1}$) can be used to identify the *cyclo*propane ring. The spectra of a number of compounds in the range 1500—780 cm.$^{-1}$ are shown in Fig. 2. These spectra are plotted by using the apparent molecular absorption coefficient (Ramsay, *J. Amer. Chem. Soc.*, 1952, **74**, 72) and allow one to compare more accurately than otherwise the relative intensities of absorption bands from one spectrum to another. α-Amyrene (VIII; R = H) and α-amyrin (VIII; R = OH) are included in Fig. 2 to facilitate comparison with a hydrocarbon which does not contain the *cyclo*propane ring and with a hydroxy-compound respectively.

It will be noticed that the hydrocarbons containing the *cyclo*propane ring do sometimes exhibit bands of medium intensity near 1010 cm.$^{-1}$. However, compounds containing hydroxyl (or ester) groups have much greater absorption in this region and it is obviously impossible to use this method of identifying *cyclo*propane rings in the presence of oxygen-containing substituents. The case of car-3-ene would also be uncertain since its strongest peak near 1010 cm.$^{-1}$ is at 973 cm.$^{-1}$, at which point α-amyrene also absorbs fairly strongly. It is possible that only those compounds in which the *cyclo*propane ring is not fully substituted exhibit the stronger absorption near 1010 cm.$^{-1}$, although Derfer *et al.* (*loc. cit.*) suggest that it is not limited to those compounds. Reid (*Chem. and Ind.*, 1953, 846) has criticised similar suggestions by Derfer *et al.* (*loc. cit.*) regarding the identification of *cyclo*butane rings.

The spectra of the above compounds have also been studied in the region of C–H bending vibrations near 1350—1480 cm.$^{-1}$ (Jones and Cole, *J. Amer. Chem. Soc.*, 1952, **74**, 5648) but no absorption which can be specifically related to the presence of the *cyclo*propane ring was found.

The author thanks Professor D. H. R. Barton, Sir John Simonsen, Dr. L. N. Owen, and Professor A. J. Birch for supplying the compounds. A Fellowship from the Nuffield Foundation is gratefully acknowledged.

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[*Received, May 3rd*, 1954.]

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*Infra-red Spectra of Natural Products. Part III.** cyclo*Artenol and Phyllanthol.*

By A. R. H. COLE.

[Reprint Order No. 5352.]

The infra-red spectra of *cyclo*artenol and phyllanthol show that these compounds have an unsubstituted CH_2 group included in their *cyclo*propane rings. This information considerably reduces the number of possible formulæ for each compound. The C–H bending region of the infra-red spectrum can be used to characterise the ring systems of new triterpenoids.

(1) cyclo*Artenol.*—Barton (*J.*, 1951, 1444) established the presence of an *iso*propylidene group in the side-chain, and of a *cyclo*propane ring, in *cyclo*artenol. These observations were confirmed by Bentley, Henry, Irvine, and Spring (*Chem. and Ind.*, 1953, 217; *J.*, 1953, 3673) who also isolated lanost-9(11)-enyl acetate (I) from the reaction of *cyclo*artanyl acetate with hydrogen chloride.

Spring and his collaborators showed that their results are most easily interpreted if the *cyclo*propane ring in *cyclo*artenol extends from $C_{(9)}$, and this allows the five possible structures (II)—(VI).†

* Part II, preceding paper.

† The author is indebted to Professor D. H. R. Barton and to Professor F. S. Spring who independently pointed out the possibility of structure (VI), after publication of a preliminary note (Cole, *Chem. and Ind.*, 1953, 946).

It has been shown in Part II * that a CH_2 group in a three-membered ring is responsible for an infra-red absorption band near 3045 cm.$^{-1}$, and this band is present in the spectra of all the *cyclo*artenol derivatives which have been studied (see Fig. 1 and the Table).

Frequency of " cyclo*propyl* CH_2 *" absorption in* cyclo*artenol and phyllanthol derivatives (cm.*$^{-1}$; CCl_4 *solution).*

*cyclo*artenol	3042	*cyclo*artanol	3042	phyllanthol	3055
*cyclo*artenone	3038	*cyclo*artenyl acetate	3036	phyllanthane	3055
*cyclo*artene	3037	*cyclo*artanyl acetate	3037	phyllanthone	3055
*cyclo*artane	3040			phyllanthyl acetate	3052

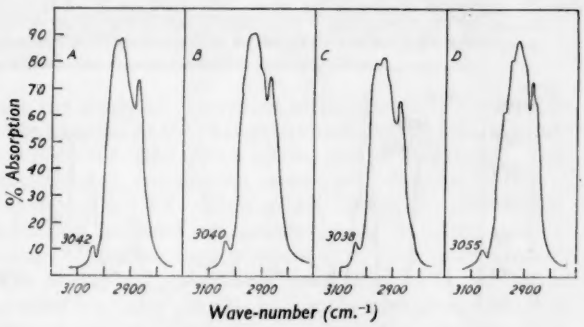
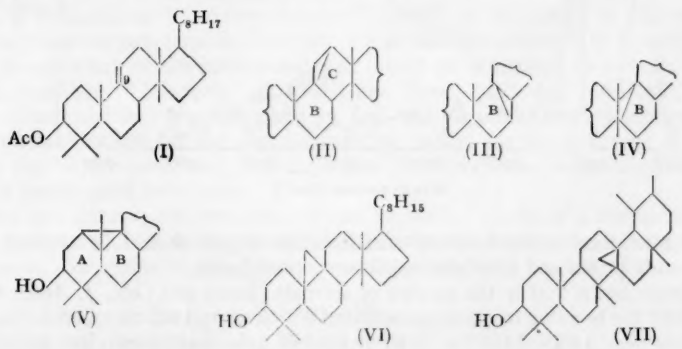


FIG. 1. *Infra-red spectra in the* C–H *stretching region* (CCl_4 *solutions*; CaF_2 *prism*).

A, *cyclo*artanol
B, *cyclo*artane
C, *cyclo*artenone
D, phyllanthane

Structures (III), (IV), and (V) are therefore eliminated but the results of the present work do not distinguish between (II) and (VI).

After this work was completed Barton, Warnhoff, and Page (*Chem. and Ind.*, 1954, 220) used other infra-red measurements to show that (VI) is the correct structure, while Henry and Spring (*Chem. and Ind.*, 1954, 189) supported this result by eliminating (II).



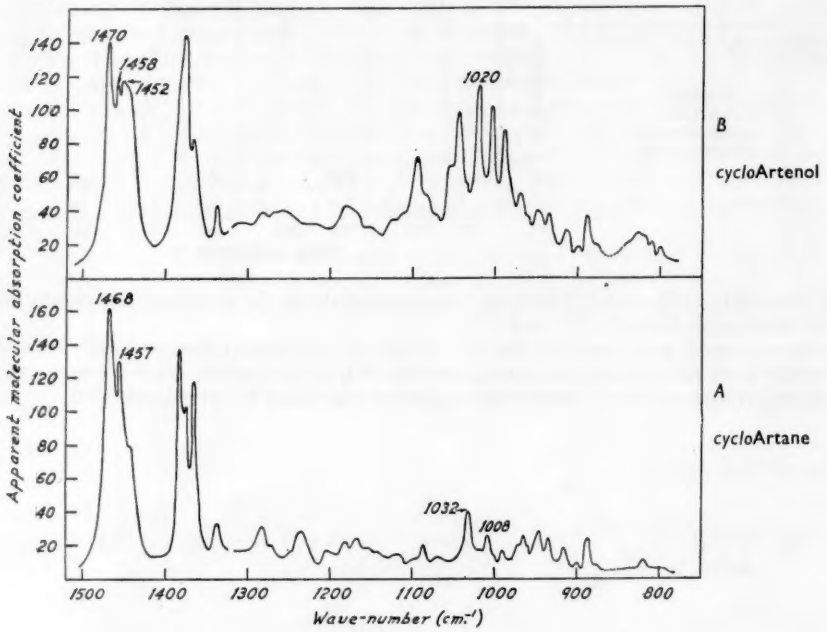
Consideration has been given in Part II * to the infra-red band near 1010 cm.$^{-1}$, suggested by Derfer, Pickett, and Boord (*J. Amer. Chem. Soc.*, 1949, **71**, 2482) to be characteristic of the *cyclo*propane ring, and it is possible that the band at 1032 cm.$^{-1}$ in the spectrum of *cyclo*artane (Fig. 2*A*) is due to this ring. However, as pointed out previously, it is extremely unwise to try to use the absorption in this region as an indication of the presence of a *cyclo*propane ring if the compound has an oxygen-containing substituent (see Fig. 2*B*).

(2) *Phyllanthol.*—Measurements in the C–H stretching region have been carried out on phyllanthol (Barton and de Mayo, *J.*, 1953, 2178) and a number of its derivatives, and the presence of the absorption band at 3052—3055 cm.$^{-1}$ (Fig. 1 and the Table) indicate that this compound also contains a CH_2 group within its three-membered ring. Later work by

Barton, Warnhoff, and Page (*loc. cit.*; *J.*, 1954, 2715) has shown that phyllanthol is represented by (VII) which agrees with the above finding.

(3) *Infra-red Absorption and the Carbon Skeleton of Triterpenoids.*—In general, most of the specific infra-red absorption bands are related to substituent groups rather than to the carbon skeleton of a triterpenoid. It would be useful in the early stages of an investigation to be able to tell whether a new compound belonged to the tetracyclic or pentacyclic series, and, if possible, to be able to distinguish between the different classes within these series. It appears that the C–H bending region of the spectrum (1350—1480 cm.$^{-1}$) will allow such a distinction to be made, at least between the tetra- and penta-cyclic types. To

FIG. 2. *Infra-red spectra in the range* 750—1500 *cm.*$^{-1}$. *The dotted region near* 850 *cm.*$^{-1}$ *is uncertain because of* CS_2 *absorption. The slight break in the curves between* 1300 *and* 1350 *cm.*$^{-1}$ *indicates the change from* CCl_4 *solvent–*CaF_2 *prism to* CS_2 *solvent–*NaCl *prism.*



obtain the maximum amount of information, this region should be studied by using a calcium fluoride prism and solutions in carbon tetrachloride.

It has been shown that in the spectra of steroids (Jones and Cole, *J. Amer. Chem. Soc.*, 1952, **74**, 5648) the bending frequency associated with five- and six-membered ring methylene groups occurs near 1450—1455 cm.$^{-1}$, while that of side-chain methylene groups lies near 1470 cm.$^{-1}$. These frequencies are indicated for *cyclo*artane and *cyclo*artenol in Fig. 2 and should be compared with those marked in Fig. 2 of the preceding paper for **3** : 5-*cyclo*-cholestane, and α-amyrene and α-amyrin. By this means it seems that the type of triterpenoid skeleton can be identified. Further work along these lines continues.

Experimental.—The experimental details were as described in the preceding paper.

The author thanks Professor D. H. R. Barton for supplying the compounds, and the Nuffield Foundation for a Fellowship.

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Adsorption from Binary Solutions of Completely Miscible Liquids. Part III. Surface Activity Coefficients of Components Adsorbed from Perfect Solutions.*

By G. A. H. Elton.

[Reprint Order No. 5418.]

On the basis of the present theory of the surface tensions of binary perfect solutions, it is shown that the surface activity coefficients of the components adsorbed at the liquid–air interface should vary linearly with bulk mole-fraction. Existing experimental data are shown to confirm this view. The theory is extended to include adsorption at the liquid–solid interface with similar theoretical results, which await experimental investigation.

The main experimental method for the study of adsorption at liquid–solid interfaces in binary solutions depends on the determination of the change in concentration which occurs when a known amount of a solution is equilibrated with a known area of adsorbent. It is then possible, subject to certain assumptions, to calculate surface mole-fraction isotherms from isotherms of concentration change (Part I *; Kipling and Tester, *J.*, 1952, 4123). Two main types of surface mole-fraction isotherm are obtained: (*a*) the surface mole-fraction of one component may always be greater than or equal to its bulk mole fraction, *i.e.*, complete preferential adsorption of this component may occur (Part II *); or (*b*) the surface mole-fraction of each component is greater than its bulk mole-fraction at low mole-fractions, and less than its bulk mole fraction at high mole-fractions, the net adsorption being zero at some intermediate mole fraction. The type of surface mole-fraction isotherm obtained in any given case depends on the energies of interaction of the adsorbed molecules with the surface of the adsorbent, and how these energies change with mole fraction. It is desirable that it should be possible ultimately to give a theoretical account of the observed surface mole-fraction isotherms, and to predict the forms of the isotherms in terms of other properties of adsorbates and adsorbent.

Adsorption at liquid–air interfaces is easier to study, as the extent of adsorption may be calculated from surface-tension data by using Gibbs's adsorption equation. Also, theories of the structure of the surface zones at liquid–air interfaces have been developed (see, *e.g.*, Guggenheim, "Mixtures," Oxford Univ. Press, 1952, pp. 166—182), based on various simplified models. We will consider first the simple theory of adsorption at a liquid–air interface, based on the quasi-crystalline model of the structure of the bulk solution and the surface zone, and then show how the theory can be modified to apply to adsorption at liquid–solid interfaces.

Adsorption at a Liquid–Air Interface: Quasi-crystalline Model of a Perfect Solution.—Gibbs's adsorption equation leads, for an ideal binary liquid mixture at temperature T, to the expression (Guggenheim and Adam, *Proc. Roy. Soc.*, 1933, *A*, **139**, 218)

$$n_B^s - \frac{x_B}{x_A} \cdot n_A^s = -\frac{1}{kT} \cdot \frac{d\gamma}{d \ln \phi_B} = -\frac{1}{kT} \cdot \frac{d\gamma}{d \ln x_B} \quad . \quad . \quad . \quad . \quad (1)$$

where n_A^s, n_B^s are the number of molecules of the components A and B respectively per cm.^{2} in the surface zone; x_A, x_B are the bulk mole fractions; γ is the surface tension; k is the Boltzmann constant; and ϕ_B is the fugacity of B. Hence values of $n_B^s - (x_B/x_A)n_A^s$ are obtainable directly from values of γ and x_B, and may be used as a convenient measure of the relative adsorption of B. (In order to obtain individual values of n_A^s, n_B^s, it is necessary to make some assumption concerning the total number of molecules in the surface zone: see p. 3814.)

For the purpose of this analysis we will adopt the quasi-crystalline model of the liquid state (see, *e.g.*, Guggenheim, *op. cit.*, p. 16), and for simplicity, confine our attention to perfect solutions, which possess the same properties as ideal solutions (Fowler and

* Part I, *J.*, 1951, 2958; Part II, *J.*, 1952, 1955.

Guggenheim, " Statistical Thermodynamics," Cambridge Univ. Press, 1939, p. 353), with the further limitation that the two species have the same molecular dimensions. We assume that the molecules in the surface zone pack in the same way as in the bulk liquid, the only difference being in composition. Finally, we assume that the difference in composition from that of the bulk liquid is confined to a single layer of molecules, an assumption which is thermodynamically consistent with equation (1) (Defay and Prigogine, *Trans. Faraday Soc.*, 1950, **46**, 199).

Using the model defined in this way, we can relate the surface tension of such a solution to the surface tension of the pure components thus (Schuchowitzky, *Acta Physicochem. U.R.S.S.*, 1944, **19**, 176; Belton and Evans, *Trans. Faraday Soc.*, 1945, **41**, 1; Guggenheim, *ibid.*, p. 150) :

$$\exp(-\gamma/N^s\boldsymbol{k}T) = x_A \exp(-\gamma_A^\circ/N^s\boldsymbol{k}T) + x_B \exp(-\gamma_B^\circ/N^s\boldsymbol{k}T) \quad . \quad . \quad (2)$$

where $N^s = n_A^s + n_B^s$, and γ_A°, γ_B° are the surface tensions of the two pure components. Hence

$$\gamma = -N^s\boldsymbol{k}T \ln (x_A\psi_A + x_B\psi_B) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where

$$\psi_A = \exp(-\gamma_A^\circ/N^s\boldsymbol{k}T) \text{ and } \psi_B = \exp(-\gamma_B^\circ/N^s\boldsymbol{k}T)$$

Differentiating (3) with respect to x_B, we obtain, for constant temperature

$$d\gamma/d \ln x_B = -N^s\boldsymbol{k}Tx_B/(c + x_B) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

where

$$c = \psi_A/(\psi_B - \psi_A) = \tfrac{1}{2}\{\coth [(\gamma_A^\circ - \gamma_B^\circ)/2N^s\boldsymbol{k}T] - 1\} \quad . \quad . \quad . \quad (5)$$

Equations (1) and (4) then give :

$$n_B^s = N^sx_B(c + 1)/(c + x_B); \; n_A^s = N^sx_Ac/(c + x_B) \quad . \quad . \quad . \quad . \quad (6)$$

$$x_B^s = x_B(c + 1)/(c + x_B); \; x_A^s = x_Ac/(c + x_B) \quad . \quad . \quad . \quad . \quad (7)$$

Hence, if f_A^s, f_B^s are the activity coefficients of A and B, respectively, in the surface layer, defined on the basis of standard states as follows :

$f_B = 1$ when $x_B = 1$; $f_B^s = 1$ when $x_B^s = 1$: $f_A = 1$ when $x_A = 1$; $f_A^s = 1$ when $x_A^s = 1$;

then we obtain

$$f_B^s = x_B/x_B^s = (c + x_B)/(c + 1); \; f_A^s = x_A/x_A^s = (c + x_B)/c \quad . \quad . \quad (8)$$

Hence, the surface activity coefficients will vary linearly with bulk mole fraction, and

$$df_B^s/dx_B = 1/(c + 1); \; df_A^s/dx_A = -1/c \quad . \quad . \quad . \quad . \quad . \quad (9)$$

Some surface-tension data are available for binary liquid mixtures which obey Raoult's law, show little or no change in heat content or volume on mixing, and have molecules of approximately equal size. We may test the theory given above by using equations (8) and (9) to calculate the theoretical variation of x_A^s, x_B^s, f_A^s, f_B^s with bulk mole fraction, and by comparing it with the "experimental" variation of these quantities, obtained from the observed surface tensions at different bulk mole fractions, using equation (1) together with the equation :

$$n_A^s + n_B^s = N^s = 1/A_A = 1/A_B \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

where A_A, A_B are the areas occupied by single molecules of A and B in the surface. These values are calculated from the densities of the liquids, Emmett and Brunauer's equation (*J. Amer. Chem. Soc.*, 1937, **59**, 1533) being used. Comparison of values of f_A^s, f_B^s obtained in the two ways is the more sensitive test of agreement (see below).

Fig. 1 shows graphs of f_A^s, f_B^s for the system chlorobenzene (A)–bromobenzene (B) at 20°, the points being calculated from smoothed surface-tension data (Kremann and

Meingast, *Sitzungsber. K. Akad. Wiss. Wien*, 1914, **123**, 821), by use of $A_A = A_B = 33{\cdot}7 \times 10^{-16}$ cm.^{2}, while the broken lines are obtained from equation (8). Fig. 2 shows similar graphs for the system H_2O(A)–D_2O(B) at 25° (Jones and Ray, *J. Chem. Physics*, 1937, **5**, 505), $A_A = A_B = 10{\cdot}5 \times 10^{-16}$ cm.^{2} being used. It is seen that in each case the points follow the calculated line quite closely.

The system benzene (A)–ethylene dichloride (B) at 14° (Whatmough, *Z. physikal. Chem.*, 1902, **39**, 129) obeys Raoult's law, but the areas of the molecules, calculated as described above, differ appreciably ($A_A = 30{\cdot}3 \times 10^{-16}$ cm.^{2}; $A_B = 28{\cdot}0 \times 10^{-16}$ cm.^{2}). Kipling and Tester's results (*loc. cit.*) lead to the values $A_A = 27{\cdot}8 \times 10^{-16}$ cm.^{2}, $A_B = 24{\cdot}4 \times 10^{-16}$ cm.^{2}. Each of these pairs of areas was used separately to calculate f_A^s, f_B^s from the smoothed surface-tension data by using the equation

$$n_A^s A_A + n_B^s A_B = 1 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

to obtain individual values of n_A^s and n_B^s from equation (1). Fig. 3 shows the two sets of values for f_A^s, f_B^s obtained in this way, together with those obtained by using $A_A = A_B = 26{\cdot}1 \times 10^{-16}$ cm.^{2} (the mean of the latter pair of areas). There is little difference

FIG. 1.

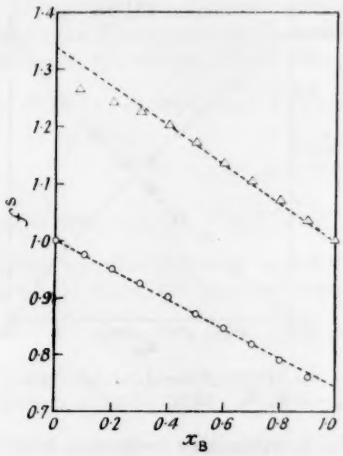
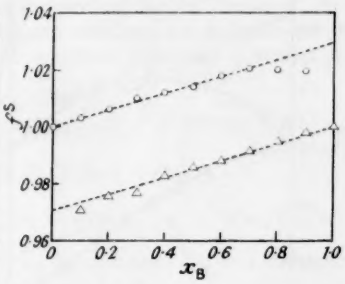


FIG. 2.



○, *A*; △, *B*.

between the results obtained by use of the various assumed areas, but considerable deviations from the theoretical lines occur, the discrepancy for each component being greatest at small mole fractions. Although the system obeys Raoult's law, there is a heat of mixing $\Delta H_m = -10$ cal./mole, and also a volume change on mixing $\Delta V_m = +0{\cdot}34\%$ (Belton and Evans, *loc. cit.*), so we may conclude that an energy of interaction between the molecules exists, and the system is not strictly ideal. Deviations from the theoeretical lines are, of course, more obvious on graphs of f_A^s, f_B^s against x_B (as given in Fig. 3) than on graphs of x_A^s, x_B^s against x_B (see Fig. 4, which gives surface mole-fraction isotherms for this system).

Deviations from the theoretical values of f_A^s, f_B^s are also found (see Fig. 5) for the system benzene (A)–chloroform (B) at 18·2° (Whatmough, *loc. cit.*). The molecular areas used in this calculation are (i) $A_A = 30{\cdot}4 \times 10^{-16}$ cm.^{2}; $A_B = 24{\cdot}1 \times 10^{-16}$ cm.^{2}, and (ii) $A_A = A_B = 27{\cdot}3 \times 10^{-16}$ cm.^{2} (the mean of the two areas). It is again seen that the surface activity coefficients obtained by using the different pairs of molecular areas agree fairly closely. Deviations from the theoretical lines again occur, and are again largest for each component at high mole fractions. Although the system follows Raoult's law closely, the heat of mixing is not zero and some association occurs (Barker and Smith, *J. Chem. Physics*, 1954, **22**, 375), so the system is not strictly ideal.

We may conclude from the study of these four systems that for binary liquid mixtures

which fulfil the requirements of a perfect solution the surface activity coefficients at liquid–air interfaces agree well with those predicted by equation (8). Surface activity coefficients for systems which obey Raoult's law owing to a cancelling of two or more " non-ideal " factors may deviate considerably from those calculated from equation (8). In each of the two systems of this type considered here, the deviations occur in such a way that the surface activity coefficient for the component which is negatively adsorbed tends towards unity at low mole-fractions, instead of towards the higher value predicted for perfect solutions. Also the surface activity coefficient of the positively adsorbed component is lower at low mole-fractions than predicted. That is, near each extreme of composition a greater degree of mixing occurs in the surface layer than that given by equation (7).

Adsorption at a Liquid–Solid Interface.—The theory of adsorption at a liquid–solid interface is more complicated than for a liquid–air interface since, for a full treatment, specific properties of the solid (*e.g.*, magnitude of lattice parameters, electronic nature of

FIG. 3.

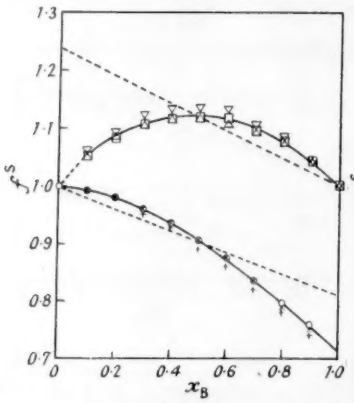
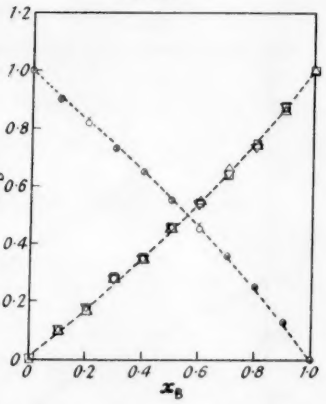


FIG. 4.



○, A; △, B, for $A_A = 27{\cdot}8$, $A_B = 24{\cdot}4$: ×, A; □, B, for $A_A = A_B = 26{\cdot}1$: +, A; ▽, B, for $A_A = 30{\cdot}3$, $A_B = 28{\cdot}0$.

adsorption sites, etc.) must be considered. For a preliminary treatment, however, various assumptions will be made, which enable a fairly simple equation to be derived.

We adopt the quasi-crystalline model of a perfect solution, and again assume that the molecules in the surface zone (confined to a single layer of molecules) pack in the same way as in the bulk liquid. These assumptions were made in the treatment of the liquid–air interface; the additional assumption for the liquid–solid interface is that when the surface layer contains n_A^s and n_B^s molecules of A and B respectively per cm.^{2}, each molecule possesses an excess of energy w_A^s or w_B^s by virtue of its interaction with the solid surface. We may then formulate the grand partition function for 1 cm.^{2} of the surface layer (Ξ^s) thus :

$$\Xi^s = \sum_{x_B^s} \frac{N^s!}{n_A^s!\, n_B^s!} (\lambda_A q_A^s)^{n_A^s} (\lambda_B q_B^s)^{n_B^s} \exp(-W^s/\boldsymbol{k}T) \quad . \quad . \quad . \quad (12)$$

where the summation is for all values of x_B^s; λ_A and λ_B are the absolute activities of A and B; q_A^s and q_B^s are the molecular partition functions per cm.^{2} of the surface layer, and

$$W^s = n_A^s w_A^s + n_B^s w_B^s = N^s[x_B^s(w_B^s - w_A^s) + w_A^s] \quad . \quad . \quad . \quad (13)$$

Using Stirling's approximation for factorials, we obtain from equation (12) :

$$\Xi^s = \sum_{x_B^s} \left(\frac{\lambda_A q_A^s}{x_A^s}\right)^{n_A^s} \left(\frac{\lambda_B q_B^s}{x_B^s}\right)^{n_B^s} \exp(-W^s/\boldsymbol{k}T) \quad . \quad . \quad . \quad . \quad (14)$$

In order to evaluate Ξ^s we replace the summation in equation (14) by its maximum term, and to determine the value of this it is necessary to make some assumption concerning the variation of w_A^s and w_B^s with x_B^s. The simplest possible assumption is that w_A^s and w_B^s are independent of the composition of the surface layer. Differentiating the summation term, and using this assumption, we find that its maximum value occurs when

$$\frac{\lambda_A q_A^s}{x_A^s} \exp(-w_A^s/kT) = \frac{\lambda_B q_B^s}{x_A^s} \exp(-w_B^s/kT) = \lambda_A q_A^s \exp(-w_A^s/kT) + \lambda_B q_B^s \exp(-w_B^s/kT) \quad . \quad (15)$$

Hence

$$\Xi^s = \left[\frac{\lambda_A q_A^s}{x_A^s} \exp(-w_A^s/kT)\right]^{n_A^s} \left[\frac{\lambda_B q_B^s}{x_B^s} \exp(-w_B^s/kT)\right]^{n_B^s} = [\lambda_A q_A^s \exp(-w_A^s/kT) + \lambda_B q_B^s \exp(-w_B^s/kT)]^{N^s} \quad . \quad (16)$$

Now

$$\Xi^s = \exp(-\gamma^x/kT); \ \lambda_A q_A^s = x_A \exp(-\gamma_A^x/N^s kT); \text{ and } \lambda_B q_B^s = x_B \exp(-\gamma_B^x/N^s kT) \quad . \quad . \quad (17)$$

where γ^x, γ_A^x, γ_B^x are the excess free energies per cm.^{2} of the surface layer, for the solution, pure A, and pure B, respectively (for analogous relations for a liquid–air interface, see, *e.g.*, Guggenheim, *op. cit.*, pp. 173—175). Hence from equations (16) and (17) we obtain

$$\exp(-\gamma^x/N^s kT) = x_A \exp[-(\gamma_A^x + N^s w_A^s)/N^s kT] + x_B \exp[-(\gamma_B^x + N^s w_B^s)/N^s kT] \quad . \quad . \quad (18)$$

$$\therefore \quad \gamma^x = -N^s kT \ln (x_A \sigma_A + x_B \sigma_B) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (19)$$

where

$$\sigma_A = \exp[-(\gamma_A^x + N^s w_A^s)/N^s kT]; \ \sigma_B = \exp[-(\gamma_B^x + N^s w_B^s)/N^s kT] \quad . \quad (20)$$

Differentiating equation (19) with respect to x_B (at constant T), and combining the result with equation (1), as for the liquid–air interface, we obtain

$$n_B^s = N^s x_B (K + 1)/(K + x_B); \ n_A^s = N^s x_A K/(K + x_B) \quad . \quad . \quad . \quad (21)$$

where $K = \sigma_A/(\sigma_B - \sigma_A)$. At present, K must be regarded as an empirical constant for a given solution and adsorbant. Also

$$x_B^s = x_B (K + 1)/(K + x_B); \ x_A^s = x_A K/(K + x_B) \quad . \quad . \quad . \quad (22)$$

and

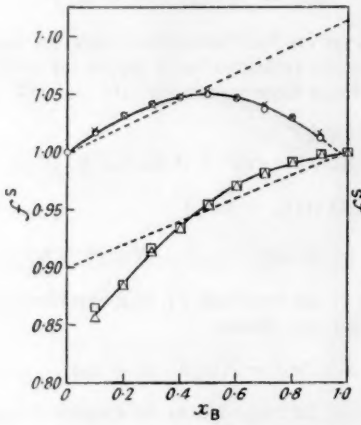
$$f_B^s = (K + x_B)/(K + 1); \ f_A^s = (K + x_B)/K \quad . \quad . \quad . \quad . \quad (23)$$

Hence this simplified theory leads to the conclusion that for systems of the type considered the surface activity coefficients at the liquid–solid interface should vary linearly with bulk mole-fraction, and that complete preferential adsorption of A should occur if K is positive, and complete preferential adsorption of B if K is negative, with no adsorption if K is zero.

Few experimental measurements which can be used to calculate surface mole-fraction isotherms at liquid–solid interfaces are reported in the literature. Although many workers (for summary, see Kipling, *Quart. Reviews*, 1951, **5**, 60) give isotherms of concentration change for binary liquid mixtures on equilibration with various solids, the surface areas of the latter are rarely given. Innes and Rowley (*J. Phys. Chem.*, 1947, **51**, 1172) give the necessary data for adsorption by charcoal from methanol–carbon tetrachloride mixtures at 25°, but the simple theory given above is not applicable to this system, as Raoult's law is not obeyed, and the molecules are of widely different size. Kipling and Tester (*loc. cit.*) studied adsorption by charcoal from benzene (A)–ethylene dichloride (B) mixtures at 20°. This system followed Raoult's law closely, and on the basis of a simple kinetic calculation Kipling and Tester deduced that complete preferential adsorption of benzene should be observed. This was not found to be the case, each component being preferentially

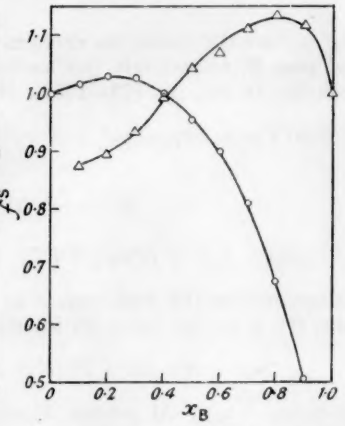
adsorbed from solutions in which its mole-fraction was low. The considerations given above indicate why the deviation from Kipling and Tester's prediction should occur. Although the system obeys Raoult's law, it is not strictly an ideal solution (see p. 3815), and we have already noted that it does not obey the " perfect " equations for adsorption at the liquid–air interface. Fig. 6 shows the calculated values of the surface activity coefficients in this system at the liquid–solid interface, Kipling and Tester's experimental results being used, with $A_A = A_B = 26{\cdot}1 \times 10^{-16}$ cm.^{2}. It is seen by comparison of Figs. 3 and 6 that replacement of the air phase by charcoal modifies the surface activity coefficients considerably. Each component when present at low mole-fractions has a higher surface activity coefficient at the liquid–solid than at the liquid–air interface. As the mole-fraction of either component is raised to high values, a decrease in the surface activity coefficient occurs, lower values being reached at the liquid–solid interface than at the liquid–air interface. At a bulk mole-fraction $x_B = 0{\cdot}41$, both surface activity coefficients are unity, and zero net adsorption occurs.

FIG. 5.



×, A; □, B, for $A_A = 30{\cdot}4$, $A_B = 24{\cdot}1$.
○, A; △, B, for $A_A = A_B = 27{\cdot}3$.

FIG. 6.



○, A; △, B.

In order that the theory of adsorption from solution by solids can be developed, it is desirable that adsorption from perfect solutions should be studied experimentally, and surface activity coefficients obtained for comparison with equation (23). It is possible that equation (23) may not correctly represent the surface activity coefficients for adsorption by a given solid, even for liquid mixtures which may be considered perfect, owing to the fact that the assumption that w_A^s, w_B^s are constants may not be valid for the system considered. For example, although there may be no net energy of interaction between the molecules of the two components in the bulk solution, their properties may be modified in the surface layer so that an energy of interaction depending on x_B^s might occur. Also, the energy of adsorption of a species may vary with x_B^s owing to the presence of adsorption sites of different energies. When experimental data are available, it may be possible to make allowance for such factors. For example, Halsey and Taylor (*J. Chem. Phys.*, 1947, **15**, 624; Halsey, *ibid.*, 1948, **16**, 931) showed that the Freundlich adsorption isotherm for gases could be derived theoretically by assuming an exponential distribution of energy among the adsorption sites. It does not, however, seem profitable at this stage to experiment with assumptions concerning the possible variation of w_A^s, w_B^s with x_B^s for the case of adsorption from solution.

BATTERSEA POLYTECHNIC, S.W.11. [*Received, May 27th*, 1954.]

Adsorption from Binary Liquid Mixtures; the Effect of Hydrogen Bonding between the Components.

By A. Blackburn and J. J. Kipling.

[Reprint Order No. 5420.]

Further studies of adsorption, by charcoal, from binary mixtures of completely miscible liquids confirm the view that the adsorbed phase is normally confined almost entirely to a monolayer. Weak hydrogen bonding between the components does not affect this result, but stronger interaction may lead to secondary adsorption on to the layer held by the solid surface. Pyridine, which is preferentially adsorbed from aqueous solutions, holds large amounts of water in a second layer by hydrogen bonding, but all material beyond this second layer is regarded as part of the bulk liquid phase.

Recent theories of adsorption from binary mixtures of completely miscible liquids have been based almost exclusively on experiments with organic compounds (Innes and Rowley, *J. Phys. Colloid Chem.*, 1947, **51**, 1172; Elton, *J.*, 1951, 2958; Kipling and Tester, *J.*, 1952, 4123; see also Kipling, *Quart. Reviews*, 1951, **5**, 60). The systems used in such work have shown relatively small molecular interaction between the two components. In many systems of practical importance, however, molecular interaction is considerable, and especially so in aqueous solutions. Water not only interacts, by hydrogen bonding, with almost all non-electrolytes with which it is completely miscible, but furthermore is itself associated to a degree which is still uncertain. It is not immediately evident to what extent these various types of association are likely to affect adsorption; indeed, the possibility of such an effect seems generally to have been overlooked until recently (cf. Fu, Hansen, and Bartell, *J. Phys. Colloid Chem.*, 1948, **52**, 374; Hansen and Fackler, *ibid.*, 1953, **57**, 634). Even these last workers have confined their investigations mainly to systems of limited miscibility.

As an approach to the problem, a study has been made of adsorption on charcoal from four systems in which the molecular interaction in the liquid phase is carefully graded from a small effect in saturated hydrocarbons to strong hydrogen bonding in an aqueous system. The four systems, in order of increasing interaction, are :

Benzene–*cyclo*hexane : this system is a convenient mixture of hydrocarbons of approximately the same molecular size.

Chloroform–acetone : this system shows a pronounced negative deviation from Raoult's law (Zawidski, *Z. physikal. Chem.*, 1900, **35**, 129), and weak hydrogen bonding between the components has been postulated (Glasstone, *Trans. Faraday Soc.*, 1937, **33**, 200; Zellhoefer, Copley, and Marvel, *J. Amer. Chem. Soc.*, 1938, **60**, 1337; Gordy, *J. Chem. Phys.*, 1939, **7**, 163).

Pyridine–ethyl alcohol : evidence for a moderate degree of hydrogen bonding in this system has been summarised elsewhere in a report on the unexpected observation that the system obeys Raoult's law at room temperature (Blackburn and Kipling, *Nature*, 1953, **171**, 174).

Pyridine–water : analogy with tertiary aliphatic amines, for which Moore and Winmill's results are available (*J.*, 1907, **91**, 1373, 1379; 1912, **101**, 1635), suggests that very considerable hydrogen bonding between the components must occur in this system. This would also explain the large difference in miscibility with water between benzene and pyridine, the molecules of which are in many ways very much alike.

Discussion

The isotherms of concentration change are presented in Figs. 1—4. For the first three systems, concentrations are expressed in mole fractions; for aqueous systems it is doubtful whether this is the appropriate unit and we have therefore used weight fractions for the fourth system.

A survey of the literature shows that, for adsorption on charcoal, such curves

normally either cross the concentration axis to give two branches, or, if there is only one branch, remain at all points concave to this axis (cf. Elton, *loc. cit.*). Figs. 1 and 2 are normal in this sense, but Figs. 3 and 4 differ in showing a point of inflexion in a one-branch curve. (The convexity of Fig. 4 would be more pronounced if it were plotted in terms of nominal mole fractions.) This type of curve has often been presented without comment for other adsorbents (*e.g.*, for alumina and other gels by Rao and Rao, *Proc. Indian Acad. Sci.*, 1936, **4**, *A*, 562), but rarely for charcoal. The only recent examples are for adsorption from aqueous solutions of the lower fatty acids (Nestler and Cassidy, *J. Amer. Chem. Soc.*, 1950, **72**, 680).

The curves of Figs. 3 and 4 suggest that there is, in the adsorbed phase, either an excess of alcohol or water, respectively, or in each case, a deficiency of pyridine, compared with the amounts expected for a normal system. Analysis of the four curves to give

Isotherms of concentration change for adsorption from:

FIG. 1. *Benzene–cyclohexane.*

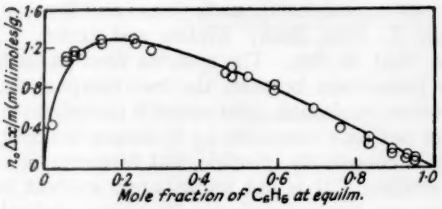


FIG. 2. *Chloroform–acetone.*

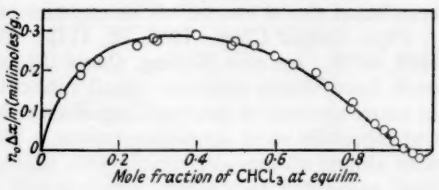


FIG. 3. *Pyridine–ethyl alcohol.*

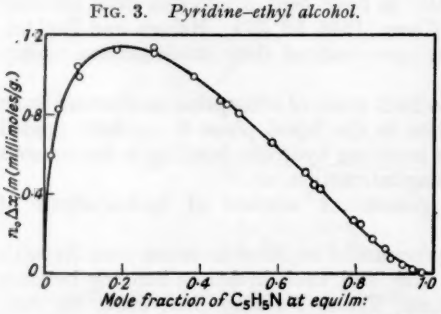
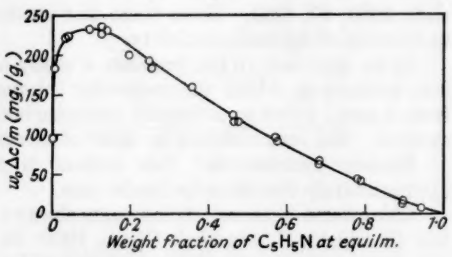


FIG. 4. *Pyridine–water.*



(Fig. 4. w_0 = wt. of original mixture; Δc = change in wt. fraction.)

adsorption isotherms for the individual components was carried out by Kipling and Tester's method (*loc. cit.*), by assuming that adsorption is confined to a monolayer and using known molecular areas. The results for the first three systems are of the expected type (Figs. 5—7). The analysis for the last system, however, gives curves showing both a maximum and a minimum (broken curves, Fig. 8). Adsorption from the vapour phase confirms these individual isotherms for the first three systems, but gives quite different results for the fourth.

For aqueous systems, the possibility of hydrogen bonding within the adsorbed phase makes it reasonable to depart from the concept of the monolayer which is advanced for normal systems. We suggest that the initial layer is able to hold further molecules, by hydrogen bonding, to form a partial or complete second layer. It is clear that pyridine is strongly adsorbed in preference to water and may be expected to cover a large fraction of the surface at nearly all concentrations. Reference to molecular models shows that there is room for each pyridine molecule to hold two water molecules in a second layer. The extent to which this occurs must be expected to vary with the composition of the liquid phase. We have therefore used the equation $z = KX(1 - c)^2$ as a crude approxim-

ation to a law of mass action expression in which z, the number of millimoles of adsorbed pyridine which have taken up water, is expressed as a function of X, the number of millimoles of unhydrated pyridine, and $(1 - c)$, the weight fraction of water in the liquid phase, K being a constant. We have also assumed that the water adsorbed directly on to the charcoal surface is in the form of dimeric molecules. The full curves shown in Fig. 8 are then obtained for $K = 5{\cdot}55$, the value, chosen empirically, which gives the best agreement with the vapour-phase results.

Adsorption (individual isotherms) from :

FIG. 5. *Benzene–cyclohexane.*

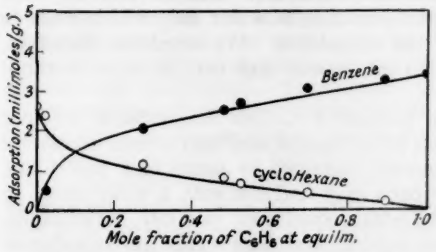


FIG. 6. *Chloroform–acetone.*

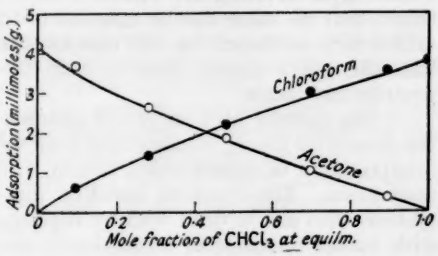


FIG. 7. *Pyridine–ethyl alcohol.*

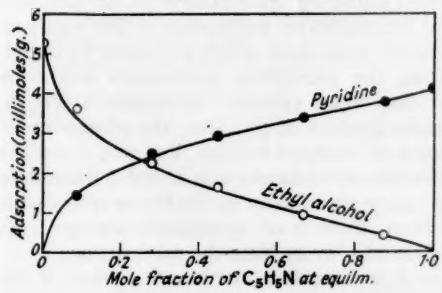
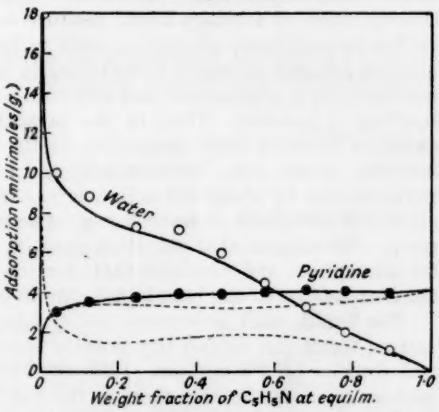


FIG. 8. *Pyridine–water.*



Figs. 5—8. Points = vapour-phase results. Curves = calc. from liquid-phase results.
Fig. 8. Broken curves = calc. from liquid-phase results, on the assumptions that water is adsorbed as monomer and that there is no interaction between components.
Full curves = calc. from liquid-phase results, on the assumptions that water is adsorbed as dimer and that there is interaction between components.

These simple assumptions could be refined; one might, for example, take account of the possibility that small amounts of pyridine may be held in the second layer by the water adsorbed in the first layer. In fact, however, such an assumption would make very little difference to the analysis.

A similar phenomenon occurring at high mole fractions of pyridine in the pyridine–alcohol system, *viz.*, the attachment of alcohol molecules to adsorbed pyridine, would explain the inflexion in Fig. 3. The effect on Fig. 7 would be to alter very slightly the shape of the individual isotherms, but the effect is too small to be confirmed with certainty. The space available in the pores of this type of charcoal limits very considerably the amount of alcohol which can be adsorbed in a second layer, whereas the much smaller water molecule can be admitted much more freely.

There is no reason for supposing that an appreciable second layer is built up in the

adsorbed phase of the chloroform–acetone system, but we would not preclude the possibility that there may be considerable interaction between the components in the adsorbed phase. The benzene–*cyclo*hexane system we regard as fitting in entirely with previous concepts for normal organic systems.

An alternative explanation of the results obtained from the pyridine–water system might be that the small water molecules penetrate to parts of the charcoal surface which are inaccessible to the larger pyridine molecules. This may well happen to some extent, as steam-activated charcoal almost certainly contains pores of about the dimensions of the water molecule. The remainder of the adsorption process could then be confined to a monolayer covering the surface available to both substances. Our calculations have shown that no value can be assigned to the area available to water only which leads to satisfactory isotherms for the components of the monolayer. We conclude, therefore, that this effect cannot alone explain the observed results and can be only a minor contributory factor.

It has recently been suggested (Hansen and Hansen, *J. Colloid Sci.*, 1954, **9**, 1*) that the monolayer theory of adsorption from solution is inadequate, and that a more consistent interpretation of experimental results is, in general, obtained in terms of a pore-filling mechanism. The equations based on this approach may find use with a wider range of systems than can be dealt with by Kipling and Tester's equations; possibly, for example, with binary mixtures of incompletely miscible liquids, and with oxide gel adsorbents. They may also be easier to use in dealing with adsorption from mixed vapours. On the other hand, a pore-filling mechanism does not account specifically for the change in concentration of a binary liquid mixture caused by adsorption. In some cases this may be due to multilayer adsorption, such as has been found by Hansen in work on partially miscible systems (in which there is clearly scope for multilayer adsorption as the region of immiscibility is approached) and with totally miscible systems in which extensive hydrogen bonding is possible. Thus in the present case, the pore-filling mechanism might be expected to apply most adequately to the pyridine–water system. Reference to Fig. 8, however, shows that, between 0·25 and 1 weight fraction of pyridine, the adsorption of pyridine rises by about 0·3 millimole/g. In pores of constant volume, this would replace about 1·3 millimoles of water per g., whereas the observed decrease is about 7 millimoles per g. We suggest that attention must be paid more specifically to the forces responsible for adsorption, and conclude that, for this system, there is an appreciable change from the composition of the bulk liquid only in the first two layers from the solid surface.

For liquids such as benzene and *cyclo*hexane it is difficult to see how the effect of the surface forces can extend significantly beyond the monolayer. Indeed the work of Cines and Ruehler (*J. Phys. Chem.*, 1953, **57**, 710) on vapour-phase adsorption of mixed hydrocarbons by silica gel leads them to the conclusion that "although some selectivity persists in the multilayers, it seems evident that selectivity is rested primarily in the monolayer. . . ." Certainly the existence of multilayer adsorption in strongly interacting systems is insufficient ground for postulating multilayer adsorption in relatively non-polar systems.

Finally, the isotherms for adsorption and desorption of benzene vapour on the type of charcoal which we have used (Davies, *Chem. and Ind.*, 1952, 160) show a very small region of hysteresis, suggesting that adsorption is essentially unimolecular, with only a very small volume of pore space available for capillary condensation or multilayer adsorption. Such a view is consistent with recent estimates of pore sizes in active charcoals made by Davies and by others.

Experimental

The adsorbent was the steam-activated coconutshell charcoal used previously (Kipling and Tester, *loc. cit.*). It was found, however, that acetone extracted ash from the charcoal, and this interfered with refractometric analysis. The charcoal was therefore freed from soluble ash by extraction with water in a Soxhlet apparatus. As far as we are aware, this method has not previously been advocated, though a similar method has been used for the purification

* We are grateful to the authors for allowing us to see the MS. of this paper before its publication.

of the shell before carbonisation (Reyerson, *Ind. Eng. Chem.*, 1925, **17**, 1114). Although our method does not remove all the ash from the charcoal, it is more convenient than the traditional acid extraction, provided (as in this case) that it is not disadvantageous to leave the water-insoluble ash in the charcoal.

Benzene and ethyl alcohol were purified as described previously. *cyclo*Hexane was fractionally distilled. The fraction used had n_D^{20} 1·4262, in agreement with the values given by Timmermans ("Physico-Chemical Constants of Pure Organic Compounds," Elsevier, London, 1950). Chloroform was purified by a modification of Gillo's method (*Ann. Chim.*, 1939, **12**, 281) and had n_D^{20} 1·4458 and d_4^{20} 1·4889, in close agreement with the values given by Timmermans.

"AnalaR" Acetone was further purified by Conant and Kirner's method (*J. Amer. Chem. Soc.*, 1924, **46**, 235) and gave n_D^{20} 1·3588. This acetone is of high purity, but is probably not as completely free from water as that of Thirion and Craven (*J. Appl. Chem.*, 1952, **2**, 210).

Pyridine (analytical reagent grade) was allowed to stand over pellets of potassium hydroxide and was then fractionated. The fraction used had n_D^{20} 1·5098 and d_4^{20} 0·9823.

The determinations were carried out at 20° by the methods previously described. For the benzene–*cyclo*hexane system, concentrations were determined interferometrically as well as refractometrically. For this purpose a Hilger–Rayleigh interferometer was used in the manner described by Bartell and Sloan (*J. Amer. Chem. Soc.*, 1929, **51**, 1657); their important observation that a well-fitting cover must be used with the cell was confirmed. A 12-v, 24-w bulb was found to be a convenient source of light.

Values of the molecular areas were based on vapour adsorption, except for water, for which a calculated value of 10 sq. Å per molecule was used, assuming a surface area for the charcoal of 540 sq. m./g., based on the observed monolayer value of 2·93 millimoles/g. for adsorption of carbon tetrachloride vapour.

We acknowledge with gratitude a grant made to the Department by Imperial Chemical Industries Limited. One of us (A. B.) is indebted to the Kingston-upon-Hull Education Committee for the grant of a Maintenance Award.

THE UNIVERSITY, HULL. [*Received, May 27th*, 1954.]

Synthetical Experiments in the Benzopyrone Series. A Synthesis of 6-Methylisoflavones.

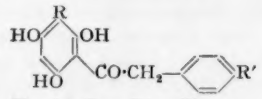
By A. C. MEHTA and T. R. SESHADRI.

[Reprint Order No. 5453.]

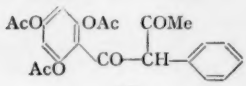
By use of acetyl chloride and pyridine at 0°, 5 : 7-dihydroxy-2 : 6-dimethyl*iso*flavone and its 4′-methoxy-derivative have been synthesised. Their 7-methyl ethers are identical with the nuclear methylation products of 5 : 7-dihydroxy-2-methyl*iso*flavone and its 4′-methoxy-derivative. By means of ethoxalyl chloride 6-methylgenistein 7 : 4′-dimethyl ether has been prepared; it is identical with the product of nuclear methylation of genistein.

IENGER, MEHTA, SESHADRI, and VARADARAJAN [*J. Sci. Ind. Res.* (*India*), 1954, **13**, *B*, 166] reported that attempts to synthesise 5 : 7-dihydroxy-2 : 6-dimethyl*iso*flavone failed, because heating benzyl 2 : 4 : 6-trihydroxy-3-methylphenyl ketone (I*b*) with sodium acetate and acetic anhydride gave the isomeric 2 : 8-dimethyl*iso*flavone, the 2-hydroxyl group of the ketone being unexpectedly more reactive. A similar result has now been obtained with the 4-methoxybenzyl ketone (I*c*). The object has, however, been achieved by employing milder conditions, namely, acetyl chloride and pyridine at 0°. In exploratory experiments, benzyl 2 : 4 : 6-trihydroxyphenyl ketone (I*a*) was employed. The immediate product was the triacetoxy-diketone (II). When it was refluxed with aqueous sodium carbonate, deacetylation and ring closure took place simultaneously, giving 5 : 7-dihydroxy-2-methyl*iso*flavone. Similarly, from benzyl 2 : 4 : 6-trihydroxy-3-methylphenyl ketone (I*b*) and its 4-methoxybenzyl analogue (I*c*), 5 : 7-dihydroxy-2 : 6-di-

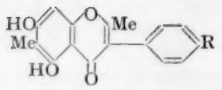
methyl*iso*flavone (III*a*) and its 4′-methoxy-derivative (III*b*) were prepared. Their partial methyl ethers (7-OMe) proved to be identical with the nuclear methylation products of 5 : 7-dihydroxy-2-methyl*iso*flavone and 2-methylgenistein 4′-methyl ether (Ienger *et al.*, *loc. cit.*). By use of ethoxalyl chloride (Baker, Chadderton, Harborne, and Ollis, *J.*, 1953,



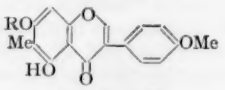
(I) (*a*) R = R′ = H
(*b*) R = Me, R′ = H
(*c*) R = Me, R′ = OMe



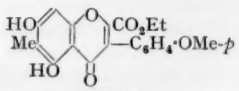
(II)



(III) (*a*) R = H
(*b*) R = OMe



(IV) R = H
(V) R = Me



(VI)

1852) with the ketone (I*c*), 6-methylgenistein 4′-methyl ether (IV) has been obtained through the intermediate ester (VI). Its 7-methyl ether (V) is identical with the nuclear methylation product of genistein prepared according to Baker and Robinson (*J.*, 1926, 2713).

Experimental

α-*Acetylbenzyl* 2 : 4 : 6-*Triacetoxyphenyl Ketone* (II).—To benzyl 2 : 4 : 6-trihydroxyphenyl ketone (I*a*) (5 g.) (Chapman and Stephen, *J.*, 1923, 404) in dry pyridine (60 c.c.) at 0° was added acetyl chloride (6·3 c.c.) with stirring. After 24 hr. at 0°, ice-water was added and the solution was extracted with ether. The extract was washed with ice-cold dilute hydrochloric acid, then with water, and dried ($MgSO_4$). Ether was distilled off and the orange-red semi-solid residue mixed with alcohol (25 c.c.) and left for 6 hr. in the refrigerator, where it became crystalline. The *diketone* crystallised from alcohol (charcoal) as colourless plates, m. p. 118—120° (3 g.). It did not give any colour with alcoholic ferric chloride and was insoluble in aqueous sodium hydroxide in the cold (Found: C, 63·8; H, 5·1. $C_{22}H_{20}O_8$ requires C, 64·1; H, 4·9%).

5 : 7-*Dihydroxy*-2-*methyl*iso*flavone*.—The diketone (2 g.) was refluxed with 10% aqueous sodium carbonate (80 c.c.) for 2 hr., then cooled and acidified. The precipitated *iso*flavone crystallised from alcohol (charcoal) as pale yellowish-brown prisms (1 g.), m. p. and mixed m. p. 228° (Baker and Robinson, *J.*, 1925, 1984).

α-*Acetylbenzyl* 2 : 4 : 6-*Triacetoxy*-3-*methylphenyl Ketone*.—The ketone (I*b*) (3 g.) (Ienger *et al.*, *loc. cit.*), pyridine (50 c.c.), and acetyl chloride (4 c.c.) were used and the product worked up as in the previous case. The *diketone* crystallised from alcohol (charcoal) as colourless rhombohedral plates, m. p. 110—112° (1·9 g.), giving no ferric reaction and insoluble in cold aqueous sodium hydroxide (Found: C, 65·1; H, 5·3. $C_{23}H_{22}O_8$ requires C, 64·8; H, 5·2%).

5 : 7-*Dihydroxy*-2 : 6-*dimethyl*iso*flavone* (III*a*).—The foregoing diketone (1 g.) was hydrolysed with 10% aqueous sodium carbonate (40 c.c.). The iso*flavone* crystallised from dilute alcohol (charcoal) as colourless rectangular plates and needles, m. p. 249—251° (0·6 g.), giving with alcoholic ferric chloride an initial violet colour which changed to deep green with excess of the reagent (Found: C, 72·1; H, 4·9. $C_{17}H_{14}O_4$ requires C, 72·3; H, 5·0%). Its 7-methyl ether was prepared by use of 1 mol. of methyl sulphate and potassium carbonate in acetone, and crystallised from alcohol as colourless needles, m. p. 188—190° alone or mixed with the nuclear methylation product of 5 : 7-dihydroxy-2-methyl*iso*flavone (Ienger *et al.*, *loc. cit.*).

5 : 7 : 4′-*Trimethoxy*-2 : 8-*dimethyl*iso*flavone*.—Benzyl 2-hydroxy-4 : 6 : 4′-trimethoxy-3-methylphenyl ketone (1 g.) (Seshadri and Varadarajan, *Proc. Indian Acad. Sci.*, 1953, **37**, *A*, 145), acetic anhydride (20 c.c.), and sodium acetate (3 g.) were refluxed at 180—185° for 12 hr. and while still hot poured over crushed ice. After 6 hr. the solid was filtered off and washed with water. The iso*flavone* crystallised from dilute alcohol as stout rectangular prisms, m. p. 182—183° (0·4 g.) (Found: C, 70·1; H, 6·1. $C_{20}H_{20}O_5$ requires C, 70·6; H, 5·9%).

5 : 7-*Dihydroxy*-4′-*methoxy*-2 : 8-*dimethyl*iso*flavone*.—Benzyl 2 : 4 : 6-trihydroxy-4′-methoxy-3-methylphenyl ketone (I*c*) (2 g.) (*idem*, *loc. cit.*), acetic anhydride (30 c.c.), and fused sodium acetate (5 g.) were refluxed at 180—185° for 12 hr. 5 : 7-*Diacetoxy*-4′-*methoxy*-2 : 8-*dimethyl*iso-

flavone crystallised from alcohol as colourless needles, m. p. 192—194° (1·1 g.) (Found : C, 67·0; H, 5·0. $C_{22}H_{20}O_7$ requires C, 66·7; H, 5·0%), giving no ferric reaction.

The diacetoxy*iso*flavone (1 g.) was hydrolysed by boiling 10% aqueous sodium carbonate (60 c.c.) for 2 hr. The *dihydroxyisoflavone* crystallised from alcohol (charcoal) as colourless needles, m. p. 239—241° (0·6 g.), which with alcoholic ferric chloride gave an initial violet colour which changed to deep green with excess of the reagent (Found : C, 69·3; H, 5·6. $C_{18}H_{16}O_5$ requires C, 69·2; H, 5·1%).

5-Hydroxy-7 : 4′-dimethoxy-2 : 8-dimethylisoflavone.—(a) *By partial demethylation.* 5 : 7 : 4′-Trimethoxy-2 : 8-dimethyl*iso*flavone (0·2 g.) in dry ether at 0° was treated with a similar solution of anhydrous aluminium trichloride (0·25 g.) with constant shaking in 20 min. After occasional shaking for 2 hr., it was set aside for 24 hr. at room temperature. Ether was then distilled off and ice and hydrochloric acid were added. The mixture was heated on a boiling-water bath for 15 min. and cooled. The yellow solid was filtered and washed with water. The iso*flavone* crystalised from alcohol (charcoal) as colourless prismatic needles, m. p. 178—179° (0·13 g.), giving with alcoholic ferric chloride an initial violet colour which changed to deep green with excess of reagent (Found : C, 70·4; H, 5·8. $C_{19}H_{18}O_5$ requires C, 69·9; H, 5·5%).

(b) *By partial methylation.* 5 : 7-Dihydroxy-4′-methoxy-2 : 8-dimethyl*iso*flavone (0·4 g.) was refluxed with methyl sulphate (0·11 c.c., 1 mol.) and potassium carbonate (1·6 g.) in acetone for 3 hr. The product crystallised from alcohol (charcoal) as needles, m. p. and mixed m. p. 178—179° (0·35 g.).

5 : 7-Dihydroxy-4′-methoxy-2 : 6-dimethylisoflavone (III*b*).—The trihydroxy-4′-methoxy-3-methyl ketone (I*c*) (3·7 g.), dry pyridine (40 c.c.), and acetyl chloride (4·6 c.c.) were used for the condensation. The intermediate diketone did not crystallise and was deacetylated with aqueous sodium carbonate. The solid product obtained on acidifying the carbonate solution crystallised from alcohol (charcoal) as colourless lance-shaped crystals, m. p. 242—244° (mixed with the isomeric 2 : 8-dimethyl derivative described above, 216°) (1·5 g.), giving with alcoholic ferric chloride an initial violet colour which changed to deep green with excess of the reagent (Found : C, 69·2; H, 5·0%). The *diacetate* (acetic anhydride and pyridine) crystallised from alcohol (charcoal) as hexahedral plates and tablets, m. p. 230—232° (Found : C, 67·1; H, 4·7. $C_{22}H_{20}O_7$ requires C, 66·7; H, 5·0%).

5-Hydroxy-7 : 4′-dimethoxy-2 : 6-dimethylisoflavone.—The dihydroxy*iso*flavone (III*b*) (0·2 g.), dry acetone (70 c.c.), methyl sulphate (0·06 c.c., 1 mol.), and potassium carbonate (0·6 g.) were refluxed for 4 hr. The product crystallised from alcohol (charcoal) as colourless flat needles and rectangular plates, m. p. 198—200° alone or mixed m. p. with the nuclear methylation product of 2-methylgenistein 4′-methyl ether (Ienger *et al.*, *loc. cit.*) (0·15 g.), giving with ferric chloride a deep pink colour which changed to deep green with excess of the reagent.

Ethyl 5 : 7-Dihydroxy-4′-methoxy-6-methylisoflavone-2-carboxylate (VI).—The ketone (I*c*) (5 g.), pyridine (70 c.c.), and ethoxalyl chloride (9 c.c.) (Southwick and Seivard, *J. Amer. Chem. Soc.*, 1949, **71**, 2535) were used for the condensation. The *ester* crystallised from benzene (charcoal) as pale yellow needles, m. p. 176—178° (4 g.) (ferric chloride reaction deep violet, changing to deep green with excess of the reagent) (Found : C, 64·5; H, 5·0. $C_{20}H_{18}O_7$ requires C, 64·9; H, 4·9%).

5 : 7-Dihydroxy-4′-methoxy-6-methylisoflavone (IV).—The above ester (0·5 g.) was refluxed with 5% aqueous sodium carbonate (60 c.c.) for 2 hr. and the solution acidified. The solid product was filtered off, washed with water, and dried. It dissolved in aqueous sodium hydrogen carbonate with effervescence. The acid (0·27 g.) was heated for 5 min. at 275°. The dark red mass was ground with aqueous sodium hydrogen carbonate, filtered, washed with water, and dried. The iso*flavone* crystallised from benzene (charcoal) as colourless rectangular prisms, m. p. 210—212° (0·21 g.) (ferric chloride reaction deep pink, changing to deep green with excess of the reagent) (Found : C, 68·1; H, 4·8. $C_{17}H_{14}O_5$ requires C, 68·4; H, 4·7%).

5-Hydroxy-7 : 4′-dimethoxy-6-methylisoflavone (V).—The above dihydroxy*iso*flavone (0·2 g.) was methylated with exactly one mol. of methyl sulphate and potassium carbonate in acetone. The dimethoxy-compound crystallised from alcohol as colourless rectangular plates, m. p. 200—201° undepressed on admixture with the nuclear methylation product of genistein (Baker *et al.*, *J.*, 1926, 2713).

Our thanks are offered to Dr. S. K. Mukerjee for microanalyses.

UNIVERSITY OF DELHI, DELHI-8. [*Received, June 9th*, 1954.]

Sugar Phosphates. Part I. Derivatives of Glucose 4 : 6-(Hydrogen Phosphate).

By J. Baddiley, J. G. Buchanan, and L. Szabó.

[Reprint Order No. 5493.]

Phosphoryl migration in the sugar phosphates is discussed in the light of recent evidence for the steric conformation of sugars. The possible participation of 6-membered cyclic phosphates as intermediates in these migrations is considered.

Cyclic phosphates of methyl and phenyl glucoside have been prepared and shown to be derivatives of glucose 4 : 6-(hydrogen phosphate) (III; R = H). Hydrogenolysis of phenyl β-D-glucoside 4 : 6-(phenyl phosphate) (IV) gave glucose 4 : 6-(hydrogen phosphate). The action of periodate on some of these compounds has been examined.

The *cyclo*hexylamine salt of glucose 4 : 6-(hydrogen phosphate) undergoes an Amadori rearrangement to the ketose derivative (IX) which, for steric reasons, is unable to assume a furanose configuration.

The structure of some other cyclic phosphates is discussed.

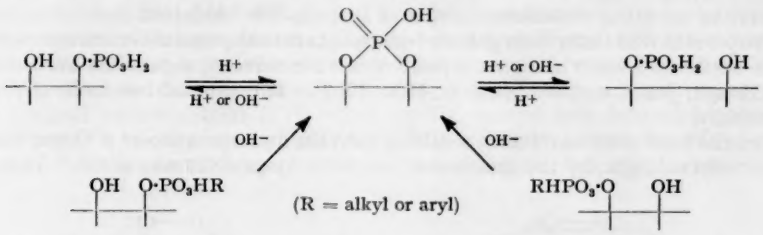
The great importance of phosphorylated intermediates in biological processes was first recognised in the field of carbohydrate metabolism. Since the first isolation of a sugar phosphate from natural sources these substances have received fairly extensive chemical and biochemical study. An excellent review of work up to 1951 is given by Leloir (*Fortschr. Chem. Org. Naturstoffe*, 1951, **8**, 47). The object of the present investigations is to study the preparation and properties of sugar phosphates, with specific reference to the configuration and conformation of the substituent groups. In particular it is proposed to examine certain group migrations and rearrangements which are believed to occur in these compounds, and to interpret the findings in the light of modern ideas of the structure of the furanose and pyranose rings (Reeves, *J. Amer. Chem. Soc.*, 1950, **72**, 1499).

Both direct and indirect evidence for migration of the phosphoryl group in sugar phosphates has been available for many years. For example, Levene and Raymond (*J. Biol. Chem.*, 1934, **107**, 75) found that attempts to synthesise xylose 3-phosphate invariably led to the formation of the 5-phosphate; also, Tankó and Robison (*Biochem. J.*, 1935, **29**, 961) suggested that migration of the phosphate group from position 6 in fructose 6-phosphate (and fructose 1 : 6-diphosphate) might explain certain changes in optical rotation observed in samples which had been subjected to acid treatment (Macfarlane and Robison, *Enzymologia*, 1937, **4**, 125; Tankó, *Acta Physiol. Acad. Sci. Hung.*, 1952, **3**, 15). Similar indirect evidence of phosphoryl migration was obtained during the mild acid hydrolysis of trehalose phosphate to glucose 6-phosphate (Tankó and Robison, *loc. cit.*; Robison and Morgan, *Biochem. J.*, 1928, **22**, 1277).

The importance of this type of migration has been largely overlooked until recently. The work of Chargaff (*J. Biol. Chem.*, 1942, **145**, 455) and of Baer and Kates (*ibid.*, 1950, **185**, 615) on the glycerophosphates and of Brown and Todd (*J.*, 1952, 52) and Cohn (*J. Amer. Chem. Soc.*, 1950, **72**, 2811) on the *a* and *b* nucleotides has demonstrated the very ready migration of phosphate groups in certain circumstances. It is clear from this work that migration is intramolecular and occurs by way of an intermediate cyclic phosphate. These isomerisations are summarised in the following scheme, in which no attempt has been made to formulate transition states or the mechanism by which the group R is eliminated.

In the glycerophosphates and nucleotides, the cyclic intermediate possess a five-membered phosphate ring. Nucleoside cyclic phosphates have been synthesised (Brown, Magrath, and Todd, *J.*, 1952, 2708) and it has been shown that they are readily hydrolysed by acids and alkalis to mixtures of the 2′- and 3′-monophosphates. Similar cyclic phosphates are formed by mild alkaline treatment of nucleotide coenzymes in which a hydroxyl group lies adjacent to a pyrophosphoric ester residue. Examples are the formation of

riboflavin-4′ : 5′ hydrogen phosphate from flavin–adenine dinucleotide (Forrest and Todd, *J.*, 1950, 3295) and glucose **1** : 2-(hydrogen phosphate) from uridine-diphosphate–glucose (Paladini and Leloir, *Biochem. J.*, 1952, **51**, 426).



The observation by Levene and Raymond (*loc. cit.*) that migration of a phosphate group from position **3** to position **5** occurred during an attempted synthesis of xylose 3-phosphate (I) has been explained by postulating a cyclic intermediate, xylose **3** : **5**-(hydrogen phosphate) (II). Until recently, authentic 6-membered phosphate rings such as that shown in

(II) were not known. It is now established that cyclic 2′ : 4′-(hydrogen phosphates) of pantothenic acid and pantetheine are produced by the action of alkali on the pyrophosphate linkage in coenzyme A (Baddiley and Thain, *J.*, 1952, 3783). These substances, which have been synthesised (*idem*, *J.*, 1951, 3421), are known to contain a 6-membered phosphate ring. A synthetic cyclic phosphate of chloramphenicol, also containing a 6-membered ring, has been described recently (Mosher, Reinhart, and Prosser, *J. Amer. Chem. Soc.*, 1953, **75**, 4899). The cyclic phosphates of pantothenic acid and its derivatives appeared to be much more stable than the nucleoside cyclic phosphates and it became of interest to examine the stability of 6-membered cyclic phosphates in the sugars, with a view to their possible rôle as intermediates in the aforementioned migrations.

The existence of a 6-membered phosphate ring in sugar derivatives will depend very much on the size of the lactol ring and on the steric relation of the esterified hydroxyl groups. For example, although **3** → **5** phosphate migration occurs readily in xylofuranose derivatives (Levene and Raymond, *loc. cit.*) it has been observed in ribofuranose derivatives. This is probably due to the larger distance between the 3- and the 5-hydroxyl group which lie on opposite sides of the planar ribofuranose ring. It has a parallel in the ready formation of **3** : **5**-cyclic acetal derivatives in the xylose series, in contrast to the behaviour of ribose and arabinose. The situation in the aldohexopyranosides is rather different. Here the chair conformation of the pyranose ring allows both glucose and galactose to form **4** : **6**-benzylidene derivatives. Two fused chair rings are present in both these derivatives.

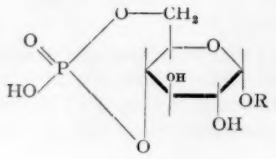
From the above considerations it seemed probable that aldohexopyranosides should form stable **4** : **6**-cyclic phosphates. The possible participation of such esters in phosphoryl migration warranted their preparation and study. When methyl α-D-glucoside was allowed to react with phenyl phosphorodichloridate in pyridine the only recognisable product was a crystalline neutral ester, produced in 10—20% yield. A phenyl group was removed by catalytic hydrogenolysis, yielding a monobasic phosphoric ester of methyl α-D-glucoside, isolated as its crystalline *cyclo*hexylamine salt. Its sodium salt slowly consumed one mol. of periodate, showing the presence of an α-glycol system. It follows that the monobasic ester is methyl α-D-glucoside **4** : **6**-(hydrogen phosphate) (III; R = Me) and the neutral ester is methyl α-D-glucoside **4** : **6**-(phenyl phosphate).

From phenyl β-D-glucoside and phenyl phosphorodichloridate a 40% yield of phenyl β-D-glucoside 4 : 6-(phenyl phosphate) (IV) was obtained. On hydrogenolysis in the presence of platinum this neutral ester yielded mainly glucose 4 : 6-(hydrogen phosphate) (III; R = H), isolated as its barium salt. The structure of this product was confirmed by its behaviour on paper chromatography and by periodate oxidation.

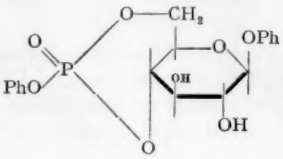
On paper it moved faster than glucose 6-phosphate in both propanol–ammonia–water and butanol–acetic acid–water and gave a positive test for reducing sugar with the *p*-anisidine spray (Hough, Jones, and Wadman, *J.*, 1950, 1702). It consumed two mols. of periodate fairly rapidly.

When the total reaction mixture resulting from the hydrogenation of (IV) was examined by paper chromatography the presence of an acidic by-product was noted. This moved

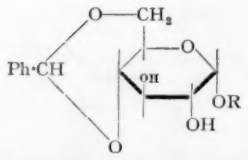
(III)



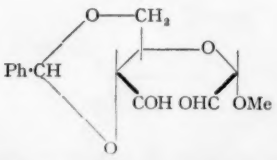
(IV)



(V)



(VI)

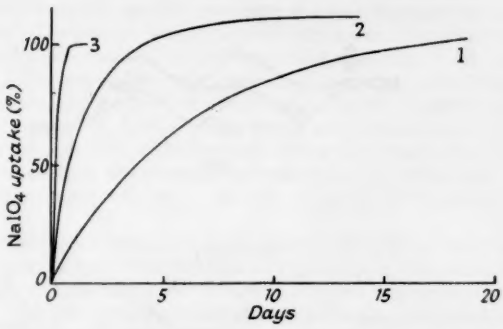


faster than glucose 4 : 6-(hydrogen phosphate) and did not possess reducing properties. When the hydrogenation was carried out with different samples of catalyst the proportion of the fast-moving substance varied and it was sometimes possible to isolate it as a crystalline *cyclo*hexylamine salt. The above properties, together with the analysis of the *cyclo*hexylamine salt, indicate that the by-product is *cyclo*hexyl β-D-glucoside 4 : 6-(hydrogen phosphate).

Marked differences were observed in the rate of periodate oxidation of the various cyclic phosphates. These differences probably arose through steric factors, and it was of some interest to compare the effects of the several possible contributory steric influences. Consequently, the rates of oxidation of several 4 : 6-cyclic phosphates of glucose were compared with those of 4 : 6-*O*-benzylidene derivatives of glucose. The three steric factors affecting periodate oxidation in the benzylidene and cyclic phosphate series are: the presence of a substituent at position 1; the presence of a 4 : 6-ring; the presence of a substituent on this ring. The combined effect of these three factors is seen in methyl α-D-glucoside 4 : 6-(phenyl phosphate) which is unaffected even by prolonged treatment with periodate. This is comparable with 7-(4 : 6-*O*-benzylidene-β-D-glucopyranosyl)theophylline which is also stable towards periodate (Harvey, Michalski, and Todd, *J.*, 1951, 2271). Both these substances bear substituents at position 1 and contain 4 : 6-rings with an attached phenyl group. After removal of the phenyl group oxidation may proceed, although rather slowly. This is shown in the case of methyl α-D-glucoside 4 : 6-(hydrogen phosphate) (see Figure). The rate of oxidation is greater in glucose 4 : 6-(hydrogen phosphate) itself. The effect of substitution at $C_{(1)}$ is also shown in the case of methyl 4 : 6-*O*-benzylidene-α-D-glucoside (V; R = Me) which is oxidised more slowly than is 4 : 6-*O*-benzylideneglucose (V; R = H). It is interesting that the dialdehyde (VI) obtained from methyl 4 : 6-*O*-benzylidene-α-D-glucoside crystallises during the oxidation.

Attempts to prepare the *cyclo*hexylamine salt of glucose 4 : 6-(hydrogen phosphate) were unsuccessful. When a solution of the free acid was neutralised with *cyclo*hexylamine and the solvent removed at a low temperature, a crystalline residue was obtained. This was shown by paper chromatography to consist of the original cyclic phosphate and another

substance, which contained both phosphorus and nitrogen and reduced methylene-blue in the cold under slightly alkaline conditions. Complete conversion into the strongly reducing substance was effected by heat. Analysis of the crystalline product indicated that 1 mol. of *cyclo*hexylamine had combined with 1 mol. of glucose 4 : 6-(hydrogen phosphate). It reduced methylene-blue and Fehling's and Benedict's solutions rapidly in the cold, and was very unstable in alkaline solution. These properties agree well with those described for substituted 1-amino-1-deoxyketoses, formed by the Amadori rearrangement of aldosylamines. We conclude that the initially formed *cyclo*hexylamine salt rearranges to an unstable glycosyl*cyclo*hexylamine (VII) which readily changes into 1-deoxy-1-*cyclo*hexylamino*keto*fructose 4 : 6-(hydrogen phosphate) (VIII). Strong support for this sequence is afforded by Helferich and Porck's observation (*Annalen*, 1953, **582**, 233) that the oxalate



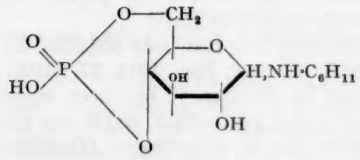
Oxidation of cyclic phosphates of glucose with periodate.

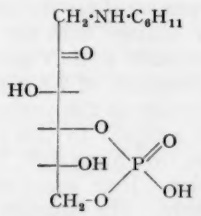
1, *Methyl* α-D-*glucoside* 4 : 6-(*hydrogen phosphate*) *at* pH 7.
2, *Methyl* 4 : 6-O-*benzylidene*-α-D-*glucoside at* pH 7.
3, *Glucose* 4 : 6-(*hydrogen phosphate*), no buffer.

of *N*-(4 : 6-*O*-benzylidene-D-glucopyranosyl)benzylamine readily undergoes an Amadori rearrangement to the corresponding 1-deoxy-1-benzylaminofructose derivative.

Although in the past it has been considered that Amadori rearrangements are confined to glycosyl derivatives of aromatic amines it is now known that this is incorrect. A number of aliphatic amines has been shown to undergo this rearrangement under suitable conditions

(VII)





(VIII)

(Hodge and Rist, *J. Amer. Chem. Soc.*, 1952, **74**, 1494; 1953, **75**, 316). It will be seen that the ketose derivative (IX) is remarkable in that, although it bears an unsubstituted hydroxyl group at position 5 and a carbonyl group at position 2, it is unable to form a furanose ring. This follows from a study of models of fructofuranose, in which the 4- and the 6-hydroxyl group lie on opposite sides of the flat ring, and hence cannot also participate in a 6-membered cyclic phosphate ring. The ultra-violet spectrum of (VIII) confirms the presence of a carbonyl group, showing a maximum at 287 mμ similar in position and intensity to those observed with penta- and tetra-*O*-acetyl*keto*fructose (Bredereck, Hoschele, and Huber, *Ber.*, 1953, **86**, 1271) and derivatives of *aldehydo*glucose (Hudson, Wolfrom, and Lowry, *J.*, 1933, 1179).

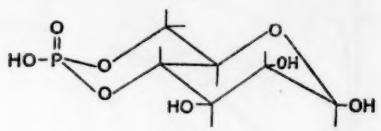
The *keto*fructose derivative (VIII) and *cyclo*hexyl β-D-glucoside 4 : 6-(hydrogen phosphate) were prepared most conveniently by heating the mixture resulting from direct hydrogenation of phenyl β-D-glucoside 4 : 6-(phenyl phosphate), after neutralisation with

*cyclo*hexylamine. The *cyclo*hexylamine salt of the *cyclo*hexyl glycoside was separated from (VIII) by means of its greater solubility in alcohol.

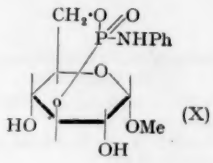
From the experiments reported in this paper it is apparent that glucopyranosides, by virtue of the equatorial conformation of hydroxyl and hydroxymethyl groups at positions 4 and 5, can form stable 4 : 6-cyclic phosphates. Furthermore, these are formed in preference to the more strained 7-membered 3 : 6-(hydrogen phosphates), even though in the latter case the 3- and the 6-hydroxyl group are *cis* to each other.

A more precise representation than (III; R = H) for glucose 4 : 6-(hydrogen phosphate) is shown in formula (IX).

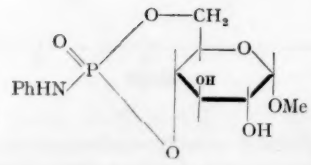
Full characterisation of the products of hydrolysis of hexopyranose 4 : 6-(hydrogen phosphates) would greatly assist the development of schemes relating to the migration of phosphoryl groups in the sugars. This problem is under investigation.



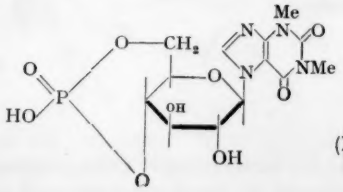
(IX)



(X)



(XI)



(XII)

Methyl α-D-glucoside yields a neutral ester by reaction with *N*-phenylphosphoramidodichloridate ($Ph{\cdot}NH{\cdot}POCl_2$) (Zeile and Kruckenberg, *Ber.*, 1942, **75**, 1127). This was formulated as methyl α-D-glucoside 3 : 6-(*N*-phenylphosphoramidate) (X). However, no evidence was presented for the presence of a 7-membered ring in the molecule. We consider that, by analogy with the compounds described in this paper, this compound is methyl α-D-glucoside 4 : 6-(*N*-phenylphosphoramidate) (XI).

A cyclic phosphate of 7-β-D-glucosyltheophylline has been obtained by the action of phosphoryl chloride on this purine glycoside (Fischer, *Ber.*, 1914, **47**, 3193). Although no structure was assigned to this compound by Fischer, it has been suggested (Kenner, *Fortschr. Chem. Org. Naturstoffe*, 1951, **8**, 96) that positions 3′ and 6′ are sterically suitable for esterification. Here again we consider the 4 : 6-(hydrogen phosphate) formulation (XII) more likely. The structure of this substance will be discussed more fully later.

Experimental

Methyl α-D-Glucoside 4 : 6-(Phenyl Phosphate).—Phenyl phosphorodichloridate (22 g.) was added with stirring at room temperature to methyl α-D-glucoside (20 g.) in pyridine (250 c.c.). The solution was kept overnight at room temperature and water (50 c.c.) was added. After 2 hr. solvent was removed *in vacuo* below 40°, chloroform and water were added, and solvents were removed again *in vacuo*. The residue was dissolved in alcohol, and water was added to opalescence (*ca.* 2 pts.). The resulting solution was passed through a column of Amberlite IR-4B (hydroxyl form) resin, and the effluent was concentrated under reduced pressure. Any oil which separated during the evaporation was removed by decantation when the volume had been reduced to about 150 c.c. The solution was then evaporated to dryness and the residue was crystallised from hot water or 0·01N-hydrochloric acid. The cyclic

phosphate (3—7 g.) had m. p. 196—197°, $[\alpha]_D^{20}$ +100·8° (*c*, 1·23 in EtOH) (Found: C, 46·7; H, 5·4. $C_{13}H_{17}O_8P$ requires C, 47·0; H, 5·1%).

Methyl α-D-*Glucoside* 4 : 6-(*Hydrogen Phosphate*).—The above phenyl ester was shaken in alcohol with hydrogen at room temperature and pressure in the presence of Adams platinum. The catalyst was filtered off and *cyclo*hexylamine was added to the solution to give pH about 8. Most of the solvent was removed *in vacuo* and ether was added until slight turbidity was produced. The solution was set aside at 0° overnight and the crystalline product was filtered off. The cyclo*hexylamine* salt (50—70%) had m. p. 228—230° (decomp.), $[\alpha]_D^{20}$ +83·1° (*c*, 1·13 in H_2O), after recrystallisation from alcohol–ether (Found: C, 44·2; H, 7·6; N, 4·0; P, 8·4. $C_{13}H_{26}O_8NP$ requires C, 43·9; H, 7·3; N, 3·9; P, 8·7%).

Phenyl β-D-*Glucoside* 4 : 6-(*Phenyl Phosphate*).—Phenyl phosphorodichloridate (25 g.) in dry pyridine (100 c.c.) was added with stirring to phenyl β-D-glucoside (35 g.) in pyridine (500 c.c.), the temperature rising to 35—40°. The mixture was kept at room temperature overnight, water (100 c.c.) was added, and the resulting solution was kept at room temperature for 2 hr., then evaporated to dryness *in vacuo*. The residue was triturated with several lots of water until only a faint smell of pyridine could be detected. The resulting solid was filtered off and recrystallised from acetic acid (250 c.c.). The crystalline *phosphate* (23·5 g.), m. p. 132—134°, resolidifying and melting at 193—194°, contained 0·5 mol. of acetic acid (Found: C, 53·8; H, 5·1; $C_{18}H_{19}O_8P,0{\cdot}5CH_3{\cdot}CO_2H$ requires C, 53·8; H, 5·0%). The acetic acid was removed by dissolving the substance in the minimum amount of hot alcohol and adding hot water until the solution became saturated at the b. p. On cooling, the phosphate crystallised (20—22 g.), m. p. 193—194°, $[\alpha]_D^{20}$ −86·3° (*c*, 1·04 in EtOH) (Found: C, 54·5; H, 4·9. $C_{18}H_{19}O_8P$ requires C, 54·8; H, 4·8%).

Glucose 4 : 6-(*Hydrogen Phosphate*).—Phenyl β-D-glucoside 4 : 6-(phenyl phosphate) (3 g.) in alcohol (100 c.c.) was reduced with hydrogen at room temperature and pressure in the presence of platinum (from 0·5 g. of platinum oxide). After filtration the acidic solution was neutralised (pH 7) with barium hydroxide solution. The precipitate which formed redissolved on standing or on addition of a little water. Alcohol (4 vols.) was added, the mixture was kept overnight at 0°, and the precipitate was removed by centrifugation. The *barium* salt (1·2 g.) was washed with alcohol, then acetone, and dried in the air. When prepared in this manner it is usually a dry white powder. However, occasionally it appeared to be hygroscopic. In this case it was allowed to remain in the air overnight and then triturated with acetone and filtered. A dry, stable product was thus obtained, which had $[\alpha]_D^{20}$ +16·1° (*c*, 3·4% in H_2O) (Found: C, 19·5; H, 4·3; P, 8·0. $C_6H_{10}O_8PBa_{\frac{1}{2}},3H_2O$ requires C, 19·8; H, 4·3; P, 8·5%).

Periodate Oxidations.—Samples of the sugar derivatives (25—250 mg.) were dissolved in suitable buffers (phosphate buffer at pH 7; acetate buffer at pH 3·6) or in water and oxidised at room temperature in the dark with an excess (20—100%) of sodium periodate. Approximately 0·01N-solutions were employed for samples of less than 100 mg., and 0·1N-solutions for the larger ones. Aliquot portions were removed periodically and periodate was determined by the usual methods.

Oxidation of Methyl 4 : 6-*O-Benzylidene*-α-D-*glucoside.* The glucoside (2·8 g.) was dissolved in hot water (750 c.c.). After cooling, sodium periodate (2·14 g.) was added and the solution was set aside for a week at 20° in the dark. The crystalline solid was filtered off, washed with water, and dried. The *dialdehyde* (2·9 g.) had m. p. 142° (Found: C, 53·2; H, 6·3. $C_{14}H_{16}O_6,2H_2O$ requires C, 53·2; H, 6·3%).

1-*Deoxy*-1-cyclo*hexylamino*keto*fructose* 4 : 6-(*Hydrogen Phosphate*).—Phenyl β-D-glucoside 4 : 6-(phenyl phosphate) (3 g.) in alcohol (100 c.c.) was reduced with hydrogen as above in the presence of Adams platinum oxide (0·3 g.). Catalyst was removed and the solution was neutralised with *cyclo*hexylamine to pH 6, refluxed under nitrogen for 5 hr., and kept overnight at room temperature. The crystalline deposit (800 mg.) was filtered off, dissolved in a little water (charcoal), and precipitated by acetone. The keto*fructose* derivative (600 mg.) had m. p. 160—165° (decomp.), $[\alpha]_D^{20}$ −39·8° (*c*, 1·41 in H_2O) (Found: C, 43·9; H, 7·4; N, 4·2; P, 9·0. $C_{12}H_{22}O_7NP$ requires C, 44·6; H, 6·8; N, 4·4; P, 9·6%).

cyclo*Hexyl* β-D-*Glucoside* 4 : 6-(*Hydrogen Phosphate*).—The alcoholic mother-liquors from the above preparations were concentrated *in vacuo* to a small volume, then set aside. The crystalline precipitate which formed was filtered off, dissolved in water (charcoal), and reprecipitated with acetone. The cyclo*hexylamine* salt of the phosphate (200 mg.) formed needles, m. p. 246—248° (decomp.) (Found: C, 51·2; H, 8·4; N, 3·5. $C_{18}H_{34}O_8NP$ requires C, 51·1; H, 8·0; N, 3·3%).

Paper Chromatography of Phosphates.—Ascending chromatograms on Whatman No. 4 paper (previously washed with 2N-acetic acid, then water, and dried) were run without temperature

control. The solvent systems were : A, butanol–acetic acid–water (4 : 1 : 5); B, *n*-propanol–ammonia–water (6 : 3 : 1). Results are tabulated.

	R_F in solvent : A	B
Glucose 4 : 6-(hydrogen phosphate)	0·14	0·29
Methyl α-D-glucoside 4 : 6-(hydrogen phosphate)	0·40	0·47
*cyclo*Hexyl β-D-glucoside 4 : 6-(hydrogen phosphate)	0·56	0·71
1-Deoxy-1-*cyclo*hexylamino*keto*fructose 4 : 6-(hydrogen phosphate)	0·53	Streak
Glucose	0·31	0·51

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Pteridine Studies. Part V. The Monosubstituted Pteridines.*

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Several new monosubstituted pteridines are described, bringing the total of such substances to 35. Previous difficulties in the replacement of hydroxyl in 7-hydroxypteridine by other groups have now been overcome.

Several methylpteridines are found, unexpectedly, to be weaker bases than the parent substance. The employment of per-acids to introduce a hydroxyl group into the 4-position of pteridine (Albert, Brown, and Cheeseman, *J.*, 1952, 4219) has been extended and used to determine the position of the methyl group in 7-methylpteridine.

MONOSUBSTITUTED pteridines are of fundamental importance in any attempt to link constitution with physical and biological properties and help in understanding the properties of naturally occurring pteridines. We now report the synthesis of 13 such substances, bringing the total to 35 (cf., *e.g.*, Albert, Brown, and Cheeseman, *J.*, 1951, 474; 1952, 1620, 4219) : all possible mono-amino-, -dimethylamino-, -chloro-, -methoxy-, and -hydroxy-pteridines are now known, and three each of the four possible mono-acetamido-, -mercapto-, -methylthio-, and -methyl-pteridines. The new substances, and some newly determined physical properties of known pteridines (Nos. 5, 22, 23, 25), are listed in the Table.

The methylpteridines were prepared by the action of glyoxal (Nos. 6, 7), methylglyoxal (No. 8), or diacetyl (Nos. 9, 10) on 4 : 5-diaminopyrimidine or its 2- or 6-methyl derivative. That No. 8 was 7(and not 6)-methylpteridine was shown by oxidation with perphthalic acid to 4-hydroxy-7-methylpteridine followed by hydrolysis of the latter to the known 2-amino-6-methylpyrazine-3-carboxylic acid (cf. Albert *et al.*, *loc. cit.*, p. 4219). Perphthalic acid has been used to convert pteridine into 4-hydroxypteridine (*idem, ibid.*), and a third example of this reaction is now provided by the similar oxidation with perbenzoic acid of 6 : 7-dimethylpteridine (No. 9) to 4-hydroxy-6 : 7-dimethylpteridine, identical with material prepared from 5 : 6-diamino-4-hydroxypyrimidine (Albert *et al.*, *J.*, 1951, 474).

Attempts to prepare 6-methylpteridine failed. In the reaction of 4 : 5-diaminopyrimidine and methylglyoxal, 7-methylpteridine was always obtained even in the presence of sodium hydrogen sulphite which had directed the methyl group to the 6-position in the similar synthesis of 4-hydroxy-6-methylpteridine (Albert *et al.*, *J.*, 1952, 4219). Neither hydrazine nor hydroxylamine influenced the orientation favourably. 4 : 5-Diaminopyrimidine has a pK_a of 6·0, but adjustment of the pH to 4 and to 8·5 to provide different ionic species gave no 6-methylpteridine. Other unsuccessful attempts include the reaction of 4 : 5-diaminopyrimidine with hydroxyiminoacetone or dichloroacetone. It was then hoped to synthesize a 6-methylpteridine having a group which could later be removed.

* Part IV, *J.*, 1953, 74.

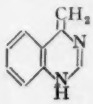
No.	Substance	Ionization [c] (H_2O; 20°) pK_a	spread ±	concn. (M)	Solubility in H_2O 20° (1 in)	100° (1 in)	Spectroscopy in water [f] $\lambda_{max.}$ (mμ)	log $\varepsilon_{max.}$	pH
1	Quinazoline [a]	3·51	0·05	0·07	—	—	—	—	—
2	4-Methyl deriv.	2·52	0·02	0·07	—	—	—	—	—
3	Quinoxaline	0·72 [d]	0·10	0·1	—	—	—	—	—
4	2-Methyl deriv.	0·95 [d]	0·08	0·1	—	—	—	—	—
5	Pteridine [b]	—	—	—	7	—	230; 298 + 309 [g]	3·65; 3·87 + 3·83	6·1
	cation [b]	4·12	0·05	0·05	—	—	286 + 300	3·88 + 3·92	1·7
	Pteridines.								
6	2-Methyl	—	—	—	9	—	230 [h]; 305 + 317 [g]	3·68; 3·92 + 3·90	6·9
	cation	4·87	0·07	0·05	—	—	248; 285 + 301	3·59; 3·88 + 3·90	2·7
7	4-Methyl	—	—	—	20	—	240 [h]; 300 + 312	3·45; 3·92 + 3·86	6·1
	cation	2·94 [e]	0·13	0·05	—	—	306	3·99	1·0
8	7-Methyl	—	—	—	6	—	235 [h]; 298 + 310	3·50; 3·98 + 3·95	6·9
	cation	3·49	0·05	0·05	—	—	304	3·99	1·4
9	6 : 7-Dimethyl	—	—	—	17	—	235 [h]; 301 + 314	3·54; 4·02 + 3·98	6·0
	cation	2·93	0·04	0·05	—	—	260; 307	3·53; 4·05	1·0
10	2 : 6 : 7-Trimethyl	—	—	—	80	—	235 [h]; 307 + 320	3·74; 4·05 + 4·03	6·5
	cation	3·76	0·04	0·05	—	—	255; 307	3·65; 4·07	1·0
11	7-Chloro	[e]	—	—	45	—	220 [h]; 303 + 309 + 316	3·92; 3·97 + 3·95 + 4·01	7·0
12	7-Methoxy	—	—	—	50	4	313 + 302; 335 [h]	3·99 + 3·95; 3·32	7·0
	cation	1·64 [d]	0·05	0·02	—	—	220; 276; 299; 330 [h]	4·33; 3·80; 3·81; 3·64	−0·4
13	7-Mercapto	—	—	—	3100	900	230; 295; 386	3·83; 3·86; 4·13	3·1
	anion	5·50	0·04	0·002	—	—	259; 302; 390	3·89; 3·84; 4·10	7·9
14	2-Methylthio	—	—	—	320	40	242; 270; 360	4·18; 4·11; 3·84	5·5
	cation	2·2 [e]	—	0·01	—	—	—	—	—
15	4-Methylthio	—	—	—	1300	180	238 + 253; 283 [h]; 354	3·95 + 3·94; 3·44; 3·93	4·9
	cation	2·59	0·06	0·04	—	—	233; 335	3·97; 4·01	0·3
16	7-Methylthio	—	—	—	200	38	240; 266 [h]; 350	3·99; 3·75; 4·15	5·0
	cation	2·49	0·03	0·01	—	—	239; 278; 343	4·22; 3·65; 4·04	0·3
17	4-Methylthio-7-methyl	—	—	—	—	—	252; 289; 346	4·03; 3·56; 3·98	5·3
	cation	<2	—	0·02	—	—	—	—	—
18	4-Mercapto-7-methyl	—	—	—	—	1500	258; 384	4·11; 4·04	4·8
	anion	7·02	0·02	0·0006	—	—	—	—	—
19	7-Amino	—	—	—	1400	170	228; 262; 334	4·26; 3·80; 4·03	5·1
	cation	2·96	0·04	0·005	—	—	217; 326	4·25; 4·00	0·6
20	7-Acetamido	[e]	—	—	—	130	228; 252; 320	4·26; 3·74; 4·18	6·7
21	7-Dimethylamino	—	—	—	6	2	240; 279; 362—366	4·19; 3·98; 4·05	5·1
	cation	2·53	0·02	0·01	—	—	245; 310—314; 361	3·95; 3·96; 4·16	0·5
22	2-Acetamido	—	—	—	—	30	230; 253; 330	4·34; 4·02; 3·95	7·0
	cation	2·67 [e]	0·05	0·02	—	—	—	—	—
23	4-Acetamido	—	—	—	—	2	223; 275 [h]; 317	4·24; 3·55; 4·05	7·0
	cation	1·21 [d]	0·02	0·1	—	—	—	—	—
24	4-Hydrazino	—	—	—	450	70	230; 244; 356	3·99; 4·01; 3·77	6·5
	cation	4·00	0·05	0·005	—	—	235; 355	4·04; 3·95	1·3
25	4-Methoxy	—	—	—	—	—	—	—	—
	cation	1·04 [d]	0·04	0·033	—	—	—	—	—

[a] Albert, Goldacre, and Phillips, *J.*, 1948, 2240. [b] Albert *et al.*, *J.*, 1951, 474. [c] Determined by method of Albert *et al.*, *J.*, 1951, 474. [d] Because the pK's are low, these are reported, for greater accuracy, as thermodynamic constants (Davies's method, *J.*, 1938, 2093). [e] Sensitive to acids. [f] Determined with Hilger "Uvispek" photoelectric spectrophotometer (1-cm. cells). [g] Fine structure. [h] Shoulder.

However, 4-hydroxy-6-methylpteridine resisted chlorination with phosphorus halides, and attempts to prepare 4-mercapto-6-methylpteridine from methylglyoxal and 4 : 5-diamino-6-mercaptopyrimidine gave only the 7-methyl isomer (No. 18). In any event, 4-mercapto- and 4-methylthio-pteridine (used as models) gave no pteridine with Raney nickel. The action of methylmagnesium iodide on 6-chloropteridine, or on 6-hydroxypteridine in dibutyl ether (140°), was also unsuccessful. 4-Hydrazinopteridine (No. 24) was prepared by heating 4-methylthiopteridine (No. 15) with hydrazine. This, the first hydrazinopteridine, was used as a model for the removal of the hydrazino-group, but copper sulphate, potassium ferricyanide, and other mild oxidizing agents caused extensive decomposition.

The Table shows that the methylpteridines (except No. 6) are weaker bases than pteridine (I). The methyl group, because of its electron-releasing nature when substituted on a carbon atom, has almost invariably been found base-strengthening in heteroaromatic nuclei. For example, 2- and 4-methylpyridine are 0·8 pK unit stronger than pyridine, and 2 : 4-dimethylpyridine is stronger still (Bruehlman and Verhoek, *J. Amer. Chem. Soc.*, 1948, **70**, 1401); 4-methylpyrimidine is 0·7 unit stronger than pyrimidine (Albert, Goldacre, and Phillips, *J.*, 1948, 2240) and only strengthening effects have been found in the glyoxaline, purine, benziminazole, and pyrazole series (respectively, Kirby and Neuberger, *Biochem. J.*, 1938, **32**, 1146; Albert and Brown, *J.*, 1954, 2060; Davies, Mamalis, Petrow, and Sturgeon, *J. Pharm. Pharmacol.*, 1951, **3**, 420; Dedichen, *Ber.*, 1906, **39**, 1831). The quinoline series has not been so well explored. Conductimetry has established that 2-methylquinoline is 0·7 unit stronger than quinoline (Goldschmidt and Salcher, *Z.*

(I)



(II)

physikal. Chem., 1899, **29**, 89). The other isomerides have not been examined by an accurate method, but 4-methylquinoline seems to show the expected base-strengthening effect (Felsing and Biggs, *J. Amer. Chem. Soc.*, 1933, **55**, 3624; Golumbic and Orchin, *ibid.*, 1950, **72**, 4145).

Accordingly we have examined 4-methylquinazoline (No. 2), a simpler analogue of No. 7, and found a marked base-weakening effect, although 2-methylquinoxaline (No. 4), a simpler analogue of No. 8, shows base-strengthening.

*exo*Methylene tautomers, *e.g.*, (II), may be involved in these base-weakening effects. Such tautomers have been isolated in the quinoline series as intermediates in the reaction of the quaternary salts of 2- and 4-methylquinoline with aldehydes (Taylor and Baker in Sidgwick's "Organic Chemistry of Nitrogen," Oxford, 1937, pp. 557—561) and are described as highly reactive substances readily oxidized in air. The anomalously weak methylpteridines are easily oxidized by air to brown resins, whereas pteridine and 2-methylpteridine are stable if light is excluded. Attempts to condense these methylpteridines with benzaldehyde caused profound decomposition (the 4- and the 7-isomer were even resinified by 0·01 equivalent of piperidine in boiling alcohol).

Former difficulties in the preparation of 7-monosubstituted pteridines from 7-hydroxypteridine have now been overcome. Whereas 7-hydroxypteridine is rapidly converted into tar by boiling phosphorus oxychloride and the addition of phosphorus pentachloride only increases the rate of destruction, it is smoothly converted into 7-chloropteridine by long refluxing with a mixture of phosphorus penta- and tri-chloride (the latter is ineffective alone, the former gives only a poor yield when chloroform or toluene replaces the trichloride). 7-Chloropteridine rapidly polymerizes (apparently by self-quaternization) in concentrated solutions above 50°. It gave 7-methoxypteridine with sodium methoxide. A comparison of the four monochloropteridines showed that the 2-isomeride is by far the most stable to hydrolysis. 7-Methoxypteridine was quantitatively converted into the sparingly soluble sodium salt of 7-hydroxypteridine with cold N-sodium hydroxide.

Although 7-hydroxypteridine is readily destroyed by phosphorus pentasulphide (Albert *et al.*, *J.*, 1952, 1620) pyridine has been found to mitigate this effect, and an optimum temperature was found for conversion into 7-mercaptopteridine. 6-Mercaptopteridine

could not be prepared by this method, nor by the action of sodium hydrogen sulphide (or thiourea) on 6-chloropteridine, profound decomposition resulting.

7-, 4-, and 2-Methylthiopteridine and 7-methyl-4-methylthiopteridine were readily prepared by the action of methyl iodide on the corresponding mercaptopteridines in cold aqueous alkali. That the methyl group was attached to sulphur and not to nitrogen was shown by the liberation of methanethiol by boiling N-sulphuric acid. A further proof in the case of 7-methylthiopteridine is provided below. 2(and 4)-Methylthiopteridine were also prepared by the action of glyoxal on 4 : 5-diamino-2(and 6)-methylthiopyrimidine. A new synthesis of 4-mercaptopteridine (from 4 : 5-dimaino-6-mercaptopyrimidine) is reported, and is preferred to the former preparation from 2-aminopyrazine-3-carboxythioamide (Albert *et al.*, *J.*, 1951, 474). 6-Methylthiopteridine could not be prepared by the action of sodium methyl sulphide on 6-chloropteridine.

7-Methylthiopteridine was readily converted into 7-aminopteridine (with alcoholic ammonia) and into 7-dimethylaminopteridine (with methanolic dimethylamine). In the latter case it was important not to heat the mixture above 60°, to prevent alkaline destruction of the dimethylaminopteridine. 7-Acetamidopteridine was obtained by acetylation of 7-aminopteridine, and the opportunity was taken to examine the physical properties of the 2- and the 4-isomer (Albert *et al.*, *J.*, 1951, 474). The 7-isomer is by far the most sensitive of the three (Nos. 20, 22, and 23) to light and to dilute acid. 6-Aminopteridine was destroyed on attempted acetylation.

Some few general remarks about monosubstituted pteridines can now be made. It has been shown that pteridine, a highly unstable substance, is stabilized by the presence of two or more electron-releasing groups (Albert *et al.*, *J.*, 1952, 4219). The monosubstituted pteridines vary from being somewhat more stable than pteridine to somewhat less. It is to be expected that pteridines bearing substituents more electron-attracting than chlorine or methylthio will be particularly unstable, and so far we have been unable to prepare a mono-nitrile or -carboxylic acid. As regards solubility, the monosubstituted pteridines obey the general rule (*idem*, *ibid.*) that pteridines having hydrogen-bonding substituents (NH_2, OH, SH) are only sparingly soluble in water and almost insoluble in other solvents, whereas pteridines lacking such substituents are highly soluble in water and in lipophilic solvents.

The ionization constants of the amino- and methoxy-pteridines are low, like those of the methyl derivatives discussed above. The mono- and di-aza-naphthalenes undergo a considerable increase in basic strength when an amino-group is inserted in the position α or γ to a ring-nitrogen atom (Albert, Goldacre, and Phillips, *J.*, 1948, 2240). Yet, in the aminopteridines this effect is either lacking, or is actually reversed (cf. No. 5 with Nos. 19 and 21; for the remaining isomers see Albert, Brown, and Cheeseman, *locc. cit.*). Again, all four methoxypteridines are weaker bases than pteridine. Although the methoxyl group can be a little base-weakening in an aromatic ring (cf. *m*-anisidine which is 0·4 pK unit weaker than aniline), it is surprising that 4-methoxypteridine (No. 25) is no less than 3 units below pteridine. These results may imply that pteridine lacks a true aromatic structure, a hypothesis already suggested by the low chemical stability and attributed to the high ratio of doubly-bound nitrogen to carbon (Albert *et al.*, *J.*, 1952, 4219).

Experimental

The yields of substances that have no definite m. p. refer to the stage at which they became chromatographically homogeneous [ascending method on papers using (separately) aqueous ammonium chloride (3%), and butanol–5N-acetic acid (7 : 3)]. R_F values were determined by the descending method in butanol–5N-acetic acid (2 : 1), with picric acid (R_F 0·80) and 4-hydroxypteridine (R_F 0·50) as controls.

Microanalyses were by Mr. P. R. W. Baker, Beckenham.

4-Methylquinazoline was prepared by Elderfield and Serlin's method (*J. Org. Chem.*, 1951, **16**, 1669), quinoxaline by Platt's (*Nature*, 1946, **157**, 439), and 2-methylquinoxaline (b. p. 126—127°/18 mm.) by Böttcher's (*Ber.*, 1913, **46**, 3084) but with 20% methylglyoxal solution in place of hydroxyiminoacetone.

2-Methylpteridine.—Acetamidine hydrochloride (142 g.) and ethyl malonate (240 g.) were

refluxed with a solution of sodium (104 g.) in absolute alcohol (2 l.) for 3 hr. The precipitate was dissolved in water (850 ml.). The 4 : 6-dihydroxy-2-methylpyrimidine precipitated by 10N-hydrochloric acid (300 ml.) was washed with water, then alcohol, and dried in air. Recrystallization from water (16 l.) gave colourless needles (70%), a considerably higher yield than given by the methods of Dox and Yoder (*J. Amer. Chem. Soc.*, 1922, **44**, 361) and Ferris and Ronzio (*ibid.*, 1940, **62**, 606). This substance (99 g.) was added during 40 min. to a well stirred mixture of nitric acid (*d* 1·5; 106 ml.) and acetic acid (270 ml.) at 15—20°. After a further 30 min., the mixture was poured on ice (1 kg.). The precipitate, washed and dried as above, was recrystallized from water (2 l.), giving 85% of colourless 4 : 6-dihydroxy-2-methyl-5-nitropyrimidine. Undiluted nitric acid (as used by Hüber and Hölscher, *Ber.*, 1938, **71**, 87) gave much lower yields. This substance was converted into 4 : 6-dichloro-2-methyl-5-nitropyrimidine according to Baddiley and Topham's directions (*J.*, 1944, 678), but the use of diethylaniline in place of dimethylaniline raised their yield (38%) to 78% (m. p. 53—54°). We have consistently found diethylaniline superior in chlorinations by phosphorus oxychloride.

This pyrimidine was converted into 4-amino-6-chloro-2-methyl-5-nitropyrimidine (77%) by methanolic ammonia in ether (Boon, Jones, and Ramage, *J.*, 1951, 96). This amine (30 g.) was treated with sodium hydrogen sulphide (as for the isomer described below), giving 4 : 5-*diamino-6-mercapto-2-methylpyrimidine* as yellow needles (92%) from 450 parts of water (Found: C, 38·5; H, 4·9; N, 35·9; S, 20·6. $C_5H_8N_4S$ requires C, 38·45; H, 5·2; N, 35·9; S, 20·5%). This substance (21 g.) was treated with Raney nickel, as for the isomer (below). Recrystallization from alcohol (380 ml.) and concentration gave 4 : 5-*diamino-2-methylpyrimidine* (80%), yellow needles, m. p. 246—248° (Found: C, 48·8; H, 6·4; N, 45·4. $C_5H_8N_4$ requires C, 48·4; H, 6·5; N, 45·1%). This diamine, treated with polyglyoxal (as below), gave 2-*methylpteridine*, sublimed at 105°/0·1 mm.), yellow leaflets, m. p. 141—142° (62%). It recrystallized from light petroleum (b. p. 60—80°; 200 parts) (Found: C, 57·4; H, 4·0; N, 38·3. $C_7H_6N_4$ requires C, 57·5; H, 4·2; N, 38·3%).

4-*Methylpteridine*.—4-Hydroxy-2-mercapto-6-methylpyrimidine (Wheeler and McFarland, *Amer. Chem. J.*, 1909, **42**, 105) was converted into 2 : 4-dihydroxy-6-methylpyrimidine (87%) by chloroacetic acid, as in the hydrolysis of thiouracil to uracil (Brown, *J. Soc. Chem. Ind.*, 1950, **69**, 353). Nitration according to Gabriel and Colman (*Ber.*, 1901, **34**, 1242) gave 88% of the 5-nitro-derivative when the temperature was kept between 5° and 10°. This product (87 g.), phosphorus oxychloride (435 ml.), and diethylaniline (105 ml.) were set aside for 20 min., then refluxed for 2 hr. (bath at 135°). The volatile compounds (300 ml.) were removed *in vacuo*, and the residue was poured slowly, with good stirring, on ice (1·5 kg.). The solution was extracted with ether (5 × 600 ml.); the extract was washed with water (200 ml.) and sodium hydrogen carbonate solution (200 ml.), dried, and freed from ether. The residual oil was distilled (125°/10 mm.), giving 2 : 4-dichloro-6-methyl-5-nitropyrimidine, m. p. 53—54° (80%). Substitution of dimethyl- for diethyl-aniline lowered the yield to 66%, and partly replaced a chlorine atom by the methylanilino-group (cf. Marshall and Walker, *J.*, 1951, 1016). Alcoholic ammonia at 0° gave 70% of 4-amino-2-chloro-6-methyl-5-nitropyrimidine, m. p. 170—171° (Gabriel and Colman, *loc. cit.*).

This amine (30 g.) was heated for 2 hr. at 95° with a saturated solution of hydrogen sulphide in 2·3N-sodium hydroxide (400 ml.). Acetic acid (about 50 ml.) was added to the hot solution, to give pH 5. After chilling overnight and filtration the precipitate was recrystallized from water (2·2 l.), giving 4 : 5-*diamino-2-mercapto-6-methylpyrimidine* (60%), as yellow needles. It recrystallized from 100 parts of water (Found: C, 38·7; H, 5·2; N, 35·7; S, 20·5%). Raney nickel catalyst (100 g., weighed wet with water) was added, in portions, to a hot mixture of the above diamine (27·5 g.), water (700 ml.), and ammonia (*d* 0·88; 28 ml.). The solution was then refluxed vigorously for 1 hr. The precipitate was extracted with boiling water (140 ml.) and the mixed filtrates were evaporated, to give 4 : 5-diamino-6-methylpyrimidine, which crystallized from *iso*butyl methyl ketone (1·2 l.) as yellow needles, m. p. 208—209° (82%). The same m. p. was obtained by Gabriel and Colman (*loc. cit.*) using a less convenient method.

4 : 5-Diamino-6-methylpyrimidine (2 g.), polyglyoxal (1·1 g.; *i.e.*, the precipitate which accumulates in bottles of syrupy glyoxal), and methanol (40 ml.) were refluxed for 20 min. The methanol was recovered at 30°, and the residue extracted with petroleum (b. p. 60—80°; 4 × 250 ml.). Evaporation of the extract, followed by sublimation at 100°/0·01 mm., gave 4-methylpteridine (60%), yellow needles, m. p. 152—153°. It recrystallized from 270 parts of light petroleum (Found: C, 57·5; H, 4·0; N, 38·3%).

7-*Methylpteridine*.—4 : 5-Diaminopyrimidine (2 g.; Brown, *J. Appl. Chem.*, 1952, **2**, 239), suspended in water (20 ml.), was added to a mixture of 20% aqueous methylglyoxal (7·4 ml.) and

sodium hydrogen sulphite solution (5 ml.; *d* 1·34). After being heated for 10 min. at 40°, the mixture was refrigerated for 2 hr. The complex was filtered off, dissolved in N-ammonia (40 ml.), and extracted with chloroform (3 × 40 ml.). The filtrate was also extracted with chloroform (3 × 40 ml.). The dried extracts were evaporated at 40°, and the product was sublimed at 95°/0·001 mm., giving **7-*methylpteridine***, m. p. 128° (60%). It recrystallized from 200 parts of light petroleum (b. p. 60—80°), giving pale yellow needles, m. p. 133—134° (Found: C, 57·9; H, 4·1; N, 38·45%). Like pteridine, all three monomethylpteridines cause sneezing.

Orientation of methyl group. 7-Methylpteridine (0·5 g.) in chloroform (2 ml.) was added to ethereal perphthalic acid (15·3 ml., 1·1 equiv.). The precipitate was recrystallized from water (14 ml.), extracted with boiling alcohol (10 ml.) to remove phthalic acid, and again recrystallized from water, giving 4-hydroxy-7-methylpteridine (70%), identical with that described by Albert *et al.* (*J.*, 1952, 4219). The identity was confirmed by degradation to 2-amino-6-methylpyrazine-3-carboxylic acid (m. p. 213°) as described there: the mixed m. p. with an authentic specimen showed no depression (2-amino-5-methylpyrazine-3-carboxylic acid, which would be given by 4-hydroxy-6-methylpteridine, has m. p. 173°).

6 : 7-*Dimethylpteridine.*—**4 : 5**-Diaminopyrimidine (0·5 g.) and diacetyl (0·43 g.) were refluxed in methanol (5 ml.) for 20 min. The solution was evaporated at 30°, and the residue sublimed at 100°/0·05 mm., giving **6 : 7-*dimethylpteridine***. It recrystallized from 300 parts of light petroleum (b. p. 60—80°) as pale yellow needles (90%), m. p. 148—149° (Found: C, 60·0; H, 5·1; N, 34·8. $C_8H_8N_4$ requires C, 60·0; H, 5·0; N, 35·0%). Oxidation with perbenzoic acid gave **6 : 7**-dimethyl-4-hydroxypteridine (75%).

4 : 5-Diamino-2-methylpyrimidine (see above) was similarly condensed with diacetyl, and purified, giving **2 : 6 : 7-*trimethylpteridine*** (90%), yellow needles, m. p. 134—135° (Found: C, 62·1; H, 5·7; N, 32·4. $C_9H_{10}N_4$ requires C, 62·0; H, 5·75; N, 32·2%). It also forms a crystalline hemihydrate.

5-Amino-**4 : 6**-dichloro-2-methylpyrimidine was synthesized as a possible intermediate for **4 : 5**-diamino-2-methylpyrimidine. **4 : 6**-Dichloro-2-methyl-5-nitropyrimidine (4 g.; see above) was added to a vigorously stirred suspension of ferrous hydroxide (from 47 g. of ferrous sulphate heptahyrdate and 55 g. of barium hydroxide octahydrate in 550 ml. of water at 75°). After ½ hr. in the boiling water-bath, the mixture was filtered, and the residue extracted with boiling water. The mixed filtrates were concentrated *in vacuo* to 150 ml. The crystals were filtered off, enriched with a chloroform extract (2 × 50 ml.) of the filtrate, recrystallized from light petroleum (b. p. 60—80°, 18 ml.) and sublimed (65°/0·01 mm.), giving colourless needles of **5-*amino*-4 : 6-*dichloro*-2-*methylpyrimidine*** (68%), m. p. 70—72° (Found: C, 33·8; H, 2·9; N, 23·6; Cl, 39·6. $C_5H_5N_3Cl_2$ requires C, 33·7; H, 2·8; N, 23·6; Cl, 39·85%).

7-*Chloropteridine.*—7-Hydroxypteridine (1 g.), phosphorus pentachloride (5 g.), and phosphorus trichloride (50 ml.) were refluxed for 7 hr., and the volatile compounds were removed in a vacuum. The residue was powdered in a chilled mortar, and covered with crushed ice (about 20 g.), then taken to pH 7 by the gradual addition of 5N-potassium hydroxide. The volume was measured (about 80 ml.) and the solution was shaken twice with that volume of chloroform. The extract was dried (Na_2SO_4) and evaporated below 20° to avoid polymerization, giving a pale solid. This was extracted with cold benzene (10 ml.), and the extract was at once concentrated to 0·5 ml. below 20°. Light petroleum (b. p. 80—100°; 1 ml.) was added and the mixture chilled overnight, giving a 30—50% yield of canary-yellow crystals, m. p. 95° (after contracting at 93°). Recrystallization from light petroleum (b. p. 40—60°; 500 parts) did not change the m. p. (Found: C, 43·3; H, 1·8; N, 33·6; Cl, 21·3. $C_6H_3N_4Cl$ requires C, 43·5; H, 1·6; N, 33·7; Cl, 21·2%). Treatment with ammonia in dry benzene (cf. Albert *et al.*, *J.*, 1952, 1620) gave chromatographically pure 7-aminopteridine (see below).

7-*Methoxypteridine.*—**7-*Chloropteridine*** (0·4 g.) in methanol (7 ml.) was added to sodium (0·06 g.) dissolved in methanol (5 ml.), refluxed for 1 hr., and evaporated under a vacuum. The residue was extracted with benzene (20 ml.), and the extract concentrated (to 1 ml.) and mixed with light petroleum (b. p. 60—80°; 2 ml.). The deposit of **7-*methoxypteridine*** was recrystallized from 5 parts of methanol, giving pale yellow crystals, m. p. 130° (70% yield)(Found: C, 51·7; H, 3·7; N, 34·4. $C_7H_6ON_4$ requires C, 51·8; H, 3·7; N, 34·5%). The m. p. was profoundly depressed by the isomers 6-methoxypteridine (m. p. 124°) and 7 : 8-dihydro-8-methyl-7-oxopteridine (m. p. 125°). It is instantly converted into the insoluble sodium salt of 7-hydroxypteridine by cold N-sodium hydroxide.

7-*Mercaptopteridine.*—Phosphorus pentasulphide (3·6 g.) was added in one portion to a solution of 7-hydroxypteridine (2 g.) in dried pyridine (60 ml.) at 100° (bath). The mixture was stirred under carbon dioxide for 2 hr., and the pyridine recovered at 80°. The dark residue was

dissolved in cold N-ammonia (200 ml.). The pH was adjusted to 8 with glacial acetic acid, and the black slime discarded. The red filtrate was taken to pH 4 with 5N-sulphuric acid. The orange precipitate (1·5 g.) was recrystallized from 170 parts of 50% aqueous dimethylformamide, giving *7-mercaptopteridine* (48%) as red needles (R_F 0·90), which decomposed above 260° (Found: C, 43·9; H, 2·4; N, 34·1; S, 19·45. $C_6H_4N_4S$ requires C, 43·9; H, 2·5; N, 34·1; S, 19·5%).

7-Methylthiopteridine.—Methyl iodide (0·15 ml.; 1·25 equiv.) was shaken with 7-mercaptopteridine (0·32 g.) dissolved in 0·5N-potassium hydroxide (1·25 equiv.) for 1 hr. at 20°. The yellow crystals were filtered off and dried at 20° [when crystallization failed to occur, the solution was extracted with cold benzene (25 + 25 ml.)]. Pale yellow *7-methylthiopteridine* (80%), recrystallized from light petroleum (b. p. 60—80°; 200 parts), had m. p. 142—143° (Found: C, 47·2; H, 3·5; N, 31·4; S, 18·2. $C_7H_6N_4S$ requires C, 47·2; H, 3·4; N, 31·4; S, 18·0%).

2-Methylthiopteridine was prepared (90%) as was the 7-isomer (from 2-mercaptopteridine monohydrate; Elion and Hitchings, *J. Amer. Chem. Soc.*, 1947, **69**, 2553), giving yellow needles, m. p. 133—136° (Found: C, 47·3; H, 3·3; N, 31·4; S, 17·9%). It was also made as follows: 4 : 5-Diamino-2-methylthiopyrimidine (0·95 g.; Albert and Brown, *J.*, 1954, 2060), polyglyoxal (0·5 g.; see above), and methanol (30 ml.) were refluxed for ½ hr. The solvent was recovered *in vacuo*. The residue was extracted with boiling light petroleum (250 + 100 ml.; b. p. 60—80°), and the extract concentrated. Further recrystallization from petroleum (230 parts) gave crystals of 2-methylthiopteridine (70%), m. p. 133—136°, undepressed by material from methylation.

4-Methylthiopteridine, prepared as was the 7-isomer, but in sodium hydroxide, was dried at 110° and recrystallized from 28 parts of benzene (2 crops), giving pale yellow crystals (90%), m. p. 191° (Found: C, 47·4; H, 3·3; N, 31·5; S, 18·0%).

4-Methylthiopteridine (Direct Synthesis).—4-Amino-6-chloro-5-nitropyrimidine (10 g.; Boon, Jones, and Ramage, *J.*, 1951, 96) was refluxed for 1½ hr. with N-sodium hydroxide (330 ml.) saturated with hydrogen sulphide. The pH was then slowly adjusted to 4—5 with acetic acid (*ca.* 30 ml.). The precipitate was extracted with boiling water (400 ml.). The crystals deposited on chilling were recrystallized from water (40 parts), giving colourless *4 : 5-diamino-6-mercaptopyrimidine* (80%), m. p. 257° (decomp.) (Found: N, 39·4; S, 22·4. $C_4H_6N_4S$ requires N, 39·4; S, 22·55%). Methyl iodide (2 ml.) was shaken vigorously for 20 min. with a solution of this pyrimidine (4 g.) in N-potassium hydroxide (32 ml.). After refrigeration, the crystals (88%) were collected and recrystallized from 12 parts of water, giving colourless needles of *4 : 5-diamino-6-methylthiopyrimidine*, m. p. 155—157° (Found: N, 35·85; S, 20·3. $C_5H_8N_4S$ requires N, 35·9; S, 20·5%). This pyrimidine (3·9 g.), dry polyglyoxal (2·3 g., see above), and methanol (110 ml.) were refluxed for ½ hr. The solid was recrystallized from ethanol (75 parts), giving 75% of 4-methylthiopteridine, m. p. 189—191°, identical with that described above.

4-Mercaptopteridine.—4 : 5-Diamino-6-mercaptopyrimidine (1·4 g.; see above) in water (45 ml.) was heated in the boiling-water bath for 15 min. with glyoxal (50% syrup; 3 ml.). The orange solid (83%) was recrystallized from water (1·1 l.) and proved identical with that made by the former method (Albert *et al.*, *J.*, 1951, 474).

7-Methyl-4-methylthiopteridine.—Methylglyoxal (17 ml. of 30% solution) in sodium hydrogen sulphite solution (42 ml.; *d* 1·34) was added to 4 : 5-diamino-6-mercaptopyrimidine (6·3 g.) and hydrated sodium sulphite (21 g.) in water (315 ml.) at 80°. After 2 days at 30°, 10N-hydrochloric acid (105 ml.) was added (5°). After 10 min., the solid was filtered off, and recrystallized from water (1500 parts), giving *4-mercapto-7-methylpteridine* (50%) as yellow crystals (R_F 0·65), decomp. above 300°, insoluble in organic solvents (Found: N, 31·3; S, 17·9. $C_7H_6N_4S$ requires N, 31·45; S, 18·0%). The orientation of the methyl group was found by hydrolysis to 2-amino-6-methylpyrazine-3-carboxylic acid (see above) by 10N-sodium hydroxide (3 hr. at 140°). Methylation, as for 7-mercaptopteridine, and recrystallization from ethanol (30 parts) gave pale needles (80%) of *7-methyl-4-methylthiopteridine*, m. p. 187—188°, which also crystallizes from benzene (Found: N, 28·9; S, 16·4. $C_8H_8N_4S$ requires N, 29·15; S, 16·7%).

7-Aminopteridine.—7-Methylthiopteridine (0·65 g.) and saturated alcoholic ammonia (10 ml.) were heated at 125° for 6 hr. The crystals which separated on cooling were recrystallized from water (140 parts), giving *7-aminopteridine* (75%) as colourless needles (R_F 0·70) which decompose above 320° (Found: C, 48·9; H, 3·3; N, 47·2. $C_6H_5N_5$ requires C, 49·0; H, 3·4; N, 47·6%). It is much more stable to hydrolysis than the 6-isomer.

7-Dimethylaminopteridine.—Methanolic dimethylamine (8 ml.; 50% solution) was added to a solution of 7-methylthiopteridine (0·36 g.) in methanol (15 ml.). After 12 hr. at 20°, the solution was refluxed for 30 min., then evaporated. The solid, dissolved in water (25 ml.), was shaken out with benzene (5 ml., discarded). The aqueous layer was evaporated and the residue recrystallized from methanol giving *7-dimethylaminopteridine* in 85% yield as pale yellow crystals,

m. p. 204°, soluble in 12 parts of boiling methanol and 19 parts of boiling ethanol (Found: C, 55·2; H, 5·2; N, 40·0. $C_8H_9N_5$ requires C, 54·8; N, 5·2; N, 40·0%). When this preparation was carried out at 125° (4 hr.) much of the dimethylaminopteridine was destroyed.

7-Acetamidopteridine.—7-Aminopteridine (0·2 g.) was refluxed with acetic anhydride (12 ml.) for 30 min. The solution was chilled and filtered, and the crystals washed with a little benzene, recrystallized from 130 parts of water and dried at 110°, giving faintly yellow *7-acetamidopteridine* (70%), R_F 0·70, decomp. above 250° (Found: C, 51·0; H, 3·9. $C_8H_7ON_5$ requires C, 50·8; H, 3·7%).

4-Hydrazinopteridine.—Hydrazine hydrate (90%; 2 ml.) was refluxed for 15 min. with 4-methylthiopteridine (2 g.) in methanol (110 ml.), and then chilled. The deposit, recrystallized from water, gave yellow needles of *4-hydrazinopteridine* (90%), m. p. 215° (decomp.) (it can also be recrystallized from *iso*amyl alcohol) (Found: C, 44·8; H, 3·8; N, 51·6. $C_6H_6N_6$ requires C, 44·45; H, 3·7; N, 51·8%). The second basic pK_a is <2. An acidic ionization, indicated by increased solubility in 0·1N-sodium hydroxide, could not be measured because of rapid decomposition to a red product. 4-Mercaptopteridine did not react with hydrazine under these conditions.

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The Pattern of Picrate Formation in the Pyridylquinoline Series.

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Diazotised 3-aminoquinoline and pyridine give a mixture of 3-2′- and 3-4′-pyridylquinoline (cf. Coates *et al.*, *J.*, 1943, 401). A possible correlation of distance between ring nitrogen atoms and mono- or di-picrate formation in the pyridylquinoline series is pointed out.

FROM the mixture of 3-pyridylquinolines arising from diazotised 3-aminoquinoline and pyridine Coates, Cook, Heilbron, Hey, Lambert, and Lewis (*J.*, 1943, 401) isolated only two picrates: a major product (A), m. p. 227—229° (free base, m. p. 101·5°), and a minor product (B), m. p. 196° (free base, m. p. 123°). Analogy (cf. Haworth, Heilbron, and Hey, *J.*, 1940, 349, 358; Butterworth, Heilbron, and Hey, *ibid.*, p. 355) suggested that (A) was 3-2′-pyridylquinoline picrate and (B) was regarded as the 3′-isomer. Hey and Williams later (*J.*, 1950, 1678) proved (A) to be the 2′-compound but found an authentic specimen of 3-3′-pyridylquinoline to have m. p. 124° (dipicrate, m. p. 222—223°). On repeating the work of Coates *et al.* they obtained the picrate identical with (A), another, m. p. 214—216°, which did not depress the melting point of an authentic specimen of the 3′-picrate, and a third, m. p. 210° (Williams, Thesis, London, 1949).

The final outcome leads to the conclusion that the second isomeride isolated by Coates *et al.* (*loc. cit.*) could be 3-3′-pyridylquinoline, though no mixed melting-point determinations were carried out with the free bases in spite of the fact that the 3′-base and Coates's unidentified isomer melt at the same temperature. This, however, would be contrary to the theoretical predictions of Wheland (*J. Amer. Chem. Soc.*, 1942, **64**, 900) and Coulson (*J. Chim. phys.*, 1948, **45**, 243), whose calculations showed that the 2′- and the 4′-isomer should be the main products of homolytic aromatic substitution in the pyridine ring. Additional ambiguity is thrown into all these arguments by the possible confusion between monopicrates and dipicrates. Unfortunately, with all the picrates prepared by Coates *et al.* analyses were carried out for nitrogen only and it is not possible to distinguish with certainty between mono- and di-picrates in this manner. The formation of mono- and di-picrates

in substituted quinolines with two basic centre has been discussed by Hey and Williams (*loc. cit.*) and by Schofield and Theobald (*J.*, 1951, 2993). The former found that 4-3′- and 4-4′-pyridylquinaldine gave dipicrates, whilst the three isomeric 2-pyridyl-lepidines and 4-3′-pyridylquinaldine formed monopicrates. Further work was clearly required to resolve these ambiguities.

First, it was found that 3-3′-pyridylquinoline gave a dipicrate which could be obtained in two forms (m. p. 210° and 224—225°). Re-examination of the mixture of 3-pyridylquinolines from diazotised 3-aminoquinoline and pyridine then showed it to contain the 2′-isomer (monopicrate, m. p. 227—228°) which would not form a dipicrate, and the 4′-isomer, m. p. 124–125° (depressed on admixture with 3-3′-pyridylquinoline, m. p. 124°), isolable as its dipicrate, m. p. 213—214°. The 3′-isomer could not be detected. These results agree with theoretical predictions. It must be concluded that the picrate (B) of Coates *et al.* (*loc. cit.*) was impure and that Williams's picrates, m. p. 214—216° and 210°, (*loc. cit.*) were both the 4′-picrate, his mixed m. p. observation being without significance. The structure of 3-4′-pyridylquinoline was confirmed by the similarity of its ultra-violet absorption spectrum with those of the 2′- and the 3′-compound.

Below are tabulated data on picrate formation in the pyridylquinoline series obtained in the present work and by other authors. The Table includes the approximate N–N distances obtained from molecular models and diagrams on the assumption that bond lengths in quinoline are the same as in naphthalene (Robertson, *Proc. Roy. Soc.*, 1933, *A*, **142**, 674; cf. dimensions of benzene and pyridine, Schomaker and Pauling, *J. Amer. Chem. Soc.*, 1939, **61**, 1769) and that the bond between the two nuclei is of the same length as in diphenyl (Dhar, *Indian J. Phys.*, 1932, **7**, 43; *Chem. Abs.*, 1932, **26**, 4517). Where two figures are given in the Table, they represent the approximate minimum and maximum values of the distances between the two ring-nitrogen atoms.

Quinoline derivative	Mono- or di-picrate	N–N distance (Å)	Compound	Mono- or di-picrate	N–N distance (Å)
2-2′-Pyridyl [b]	Mono	3·0—3·7	2-2′-Pyridyl-lepidine [c]	Mono	3·0—3·7
2-3′-Pyridyl [c]	Mono	4·3—4·95	2-3′-Pyridyl-lepidine [c]	Mono	4·3—4·95
2-4′-Pyridyl [c]	Mono	5·12	2-4′-Pyridyl-lepidine [c]	Mono-	5·12
3-2′-Pyridyl [d]	Mono	4·4—5·0	4-2′-Pyridylquinoline [e]	Mono	5·2
3-3′-Pyridyl [d]	Di	5·8—6·25	4-3′-Pyridylquinoline [e]	Di	6·5
3-4′-Pyridyl [d]	Di	6·6	4-4′-Pyridylquinoline [e]	Di	7·1
8-2′-Pyridyl [a]	Mono	2·5—4·2	4-2′-Pyridylquinaldine [e]	Mono	5·2
8-3′-Pyridyl [a]	Mono	3·7—5·1	4-3′-Pyridylquinaldine [e]	Di	6·5
8-4′-Pyridyl [a]	Mono	4·8	4-4′-Pyridylquinaldine [e]	Di	7·1
6-3′-Pyridyl [a]	Di	7·95			

[a] Coates *et al.*, *loc. cit.* [b] Smirnoff, *Helv. Chim. Acta*, 1921, **4**, 802. [c] Hey and Williams, *loc. cit.* [d] Present work. [e] Schofield and Theobald, *loc. cit.*

There thus appears to be a correlation of picrate formation with the distance between the nitrogen atoms. When this distance is lower than, or equal to, 5·2 Å, monopicrates are formed, whereas if the minimum distance is greater than 5·8 Å, dipicrates are formed. It should be mentioned, however, that 6-methoxy-5(or 7)-2′-pyridylquinoline forms a monopicrate (Coates *et al.*, *J.*, 1943, 406), as also do some lutidylquinolines (Cook, Heilbron, and Steger, *J.*, 1943, 413), which would be expected to form dipicrates, although these picrates were analysed for nitrogen only so that ambiguities may arise. Steric factors may also be in operation.

Experimental

The spectrophotometric measurements were carried out with a Unicam SP. 500 instrument, absolute ethanolic solutions of the bases (*ca.* 3 mg. per l. of solution) being used.

3-3′-Pyridylquinoline Dipicrates.—3-3′-Pyridylquinoline ($\lambda_{max.}$ 210, 248 mμ; $10^{-3}\varepsilon$ 11·9, 31·7) in acetone was treated with one mol. of picric acid in acetone. Recrystallisation from the same solvent gave *3-3′-pyridylquinoline dipicrate* as matted yellow needles, m. p. 210° (Found: C, 47·7; H, 2·6; N, 16·5. $C_{11}H_{10}N_2,2C_6H_3O_7N_3$ requires C, 47·5; H, 2·5; N, 16·8%). This was boiled with an excess of picric acid in acetone, whereupon 3-3′-pyridylquinoline dipicrate

separated as small, dark-yellow needles, m. p. 224—225°, after sintering at 180° (Found: C, 47·8; H, 3·1%). Hey and Williams (*loc. cit.*) report m. p. 222—223°, after sintering at 180°, for 3-3′-pyridylquinoline dipicrate.

Action of Diazotised 3-Aminoquinoline on Pyridine.—The suspension of the hydrochloride from 3-aminoquinoline (18·5 g.), concentrated hydrochloric acid (50 c.c.), and water (25 c.c.) was cooled to 5°, sodium nitrite (9 g.) in water (25 c.c.) added as quickly as possible below 10°, and the solid diazonium salt dissolved by addition of ice and water (400 g.). The solution was introduced during 1 hr. into pyridine (500 c.c.) stirred at 50°. The mixture was made alkaline with ammonia, and pyridine removed in steam. The residual tar was extracted with boiling benzene (charcoal), and the dried ($MgSO_4$) extract was distilled. The pyridylquinolines, b. p. 145—170°/0·02 mm., formed a golden-yellow oil (10·5 g.) which solidified. The bases (10 g.) in acetone (200 c.c.) were treated with a solution of picric acid (15 g.) in the same solvent (100 c.c.). The picrates were collected and the mother-liquor (A) was preserved. Recrystallisation of the picrates from *cyclo*hexanone gave almost pure 3-2′-pyridylquinoline monopicrate (10·1 g.). On recrystallisation from the same solvent it was obtained as soft yellow needles, m. p. 227—228° (Found: C, 55·1; H, 2·6. Calc. for $C_{14}H_{10}N_2,C_6H_3O_7N_3$: C, 55·2; H, 3·0%). It remained unchanged when boiled with a solution of an excess of picric acid. Decomposition of the picrate with hot 10% aqueous sodium hydroxide, extraction with hot benzene, evaporation of the dried extract, and recrystallisation of the residue from light petroleum (b. p. 60—80°) containing a little benzene, gave 3-2′-pyridylquinoline as stout prisms, m. p. 101·5° ($\lambda_{max.}$ 204, 246 mμ, $10^{-3}\varepsilon$ 9·5, 28·2). Coates *et al.* (*loc. cit.*) give m. p. 227—229° for the picrate and m. p. 101·5° for the free base. The initial *cyclo*hexanone mother-liquor was evaporated under a vacuum on the water-bath. The residual picrate was recrystallised from acetone, giving a product (1·6 g.), m. p. 201—203°. The free base, liberated as before, was recrystallised from light petroleum (b. p. 60—80°) containing a trace of benzene, and was obtained as delicate white plates of *3-4′-pyridylquinoline* ($\lambda_{max.}$ 206, 252 mμ; $10^{-3}\varepsilon$ 23·4, 38·3), m. p. 124—125° (Found: C, 81·4; H, 4·7. $C_{14}H_{10}N_2$ requires C, 81·5; H, 4·9%) depressed on admixture with the 2′- or the 3′-base. The *dipicrate* separated from acetone as small yellow needles, m. p. 213—214° (Found: C, 47·5; H, 2·5; N, 16·8. $C_{14}H_{10}N_2,2C_6H_3O_7N_3$ requires C, 47·5; H, 2·5; N, 16·9%). Partial evaporation of the initial acetone mother-liquor (A) gave a further amount (1·3 g.) of 3-4′-pyridylquinoline dipicrate, m. p. 210·5° (free base, m. p. 124—125°, undepressed on admixture with a sample obtained as above).

The initial mixture of bases from the vacuum-distillation (3 g.) was dissolved in a small volume of benzene and chromatographed on a column of alumina (70 g., 6½″ × 1″). Elution with benzene and collection of 25-ml. portions gave 3-2′-pyridylquinoline (0·20 g.), m. p. 94·5—95·5°, undepressed on admixture with an authentic specimen. Further elution with benzene gave a mixture of bases.

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Indoles. Part I. The Formylation of Indole and Some Reactions of 3-Formylindole.

By G. F. Smith.

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The yield of 3-formylindole by the formylation of indole by phosphorus oxychloride in excess of dimethylformamide has been raised to 95·5%, and the mechanism of this reaction studied. When pyrrole is formylated in this way an 83% yield of 2-formylpyrrole is obtained. A new method for the synthesis of urorosein salts is described.

Tyson and Shaw (*J. Amer. Chem. Soc.*, 1952, **74**, 2273) describe the conversion of indole into 3-formylindole in 72% yield, by use of a mixture of phosphorus oxychloride and dimethylformamide. By means of some simplifications in the procedure, a 95·5% yield of very pure product has now been obtained. The mechanism of this reaction is of interest, and has been studied in some detail.

Only one mol. of phosphorus oxychloride is essential for the reaction, but an excess of dimethylformamide is necessary simply to keep the reaction mixture reasonably fluid. In one experiment in which the ratio $POCl_3$: indole was 1 : 4, about 70% of the indole was recovered and 18% of pure 3-formyl derivative was isolated, the remaining 12% consisting of a mixture from which an unidentified product, m. p. 249—253°, was isolated. This experiment clearly indicates the necessity of a phosphorus oxychloride : indole ratio of 1 : 1; it is noteworthy that phosphorus oxychloride and dimethylformamide form a 1 : 1 complex, which begins to dissociate at about 100°/10 mm.

The clear viscous reaction mixture obtained by the addition of 1 mol. of indole to phosphorus oxychloride in excess of dimethylformamide, on being diluted with more solvent, shows two absorption maxima: 345 mμ, log ε 4·19; 276 mμ, log ε 3·96 (below 276 mμ absorption by solvent begins to interfere). Very similar absorption is shown by an aqueous solution of the reaction mixture: 337·5 mμ, log ε 4·21; 274 mμ, log ε 3·93; 268 mμ, log ε 3·95; 253 mμ, log ε 4·04; 244 mμ, log ε 4·03, and this is unchanged on careful neutralisation of the aqueous solution. The absorption changes, however, in alkaline solution to 324·5 mμ, log ε 4·09; 265 mμ, log ε 4·19, which is practically identical with that of an alkaline solution of 3-formylindole (Fig. 1, curve *b*).

The reaction intermediate is thus not decomposed by water; it is relatively stable in acid or neutral solution; in alkaline solution it is hydrolysed to 3-formylindole.

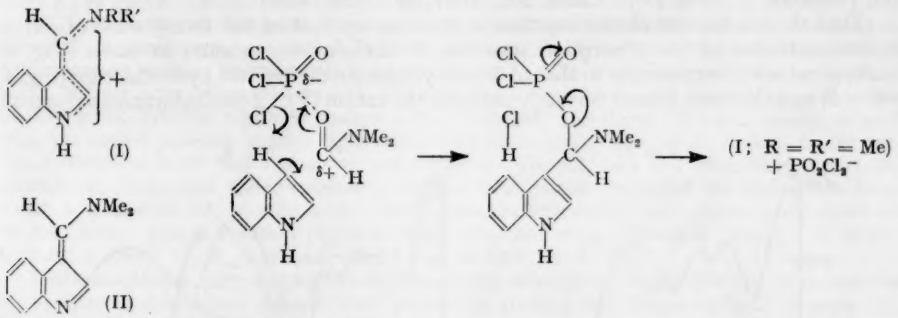
The hypothesis that the intermediate might be the mesomeric cation (I; R = R′ = Me) was soon confirmed. The aqueous neutralised solution was basified at −5° and rapidly extracted with chloroform: this yielded a crystalline base (absorption spectrum, Fig. 3, curve *a*), the absorption spectrum of the stable hydrochloride of which (Fig. 2, curve *a*) was identical with that of the reaction intermediate. Structure (II), 3-dimethylaminomethyleneindolenine, has been assigned to the base on the basis of its quantitative hydrolysis in boiling water to 3-formylindole and dimethylamine, its reduction to gramine by means of lithium aluminium hydride in ether, and the combustion analysis.

With (I; R = R′ = Me) as the structure of the reaction intermediate, the most plausible mechanism for the formylation seems to be that shown below. The $PO_2Cl_2^-$ ion is hydrolysed in water to orthophosphoric and hydrochloric acid.

The alkaline hydrolysis of (I; R = R′ = Me) almost certainly involves attack at the exocyclic carbon atom by hydroxyl ion to yield the unstable aldehyde ammonia, which then breaks down to dimethylamine and 3-formylindole.

That the hydrogen chloride formed in the formylation does not participate in the reaction was demonstrated when a 1 : 1 mixture of dry hydrogen chloride and indole in excess of dimethylformamide was kept at 70° for 15 min.; 83% of the indole was recovered and 3-formylindole was not detected. This also means that protonated solvent does not act as a formylating agent.

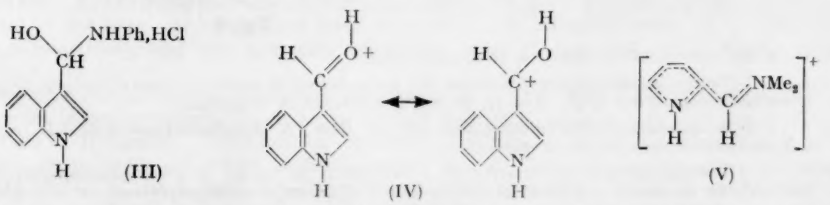
Thionyl chloride in excess of dimethylformamide also reacts very vigorously with indole, but the reaction is not clean even at 25—30°: the absorption spectrum of the filtered aqueous solution indicates only a 45—50% yield of (I; R = R′ = Me).



An attempted synthesis of the mesomeric cation (I; R = R′ = Me) by methylation of 3-methyliminomethylindole was unsuccesful. 3-Formylindole reacts very readily with aqueous methylamine, to give an amorphous base which does, however, yield a stable crystalline hydrochloride the absorption spectrum of which (Fig. 2, *b*) is very similar in type to that of (I; R = R′ = Me). Methylation of the base with methyl iodide or methyl sulphate, in the presence or absence of solvent, failed to yield a homogeneous crystalline product.

Majima and Kotake (*Ber.*, 1925, **58**, 2037) reported that interaction of 3-formylindole and aniline in the presence of hydrochloric acid gave a yellow compound, which they considered to be (III), converted by cold alkali into 3-phenyliminoindole. These two compounds have been prepared by a modified procedure, and there can be little doubt that the salt has the cation (I; R = H, R′ = Ph) (for absorption spectrum, measured in dioxan, see Fig. 2, *c*).

The salt is rapidly hydrolysed in water or alcohol to 3-formylindole and aniline hydrochloride, the aqueous solution becoming colourless in less than one minute. This ease of hydrolysis is to be contrasted with the stability of aqueous solutions of (I; R = R′ = Me) and (I; R = H, R′ = Me).



Majima and Kotake (*loc. cit.*) gave the red needles, formed when the yellow hydrochloride is warmed with hydrochloric acid, the molecular formula $C_{15}H_{17}O_2N_2Cl$, but no structure was proposed. This compound is obviously urorosein chloride, which is formed by the action of hydrochloric acid on 3-formylindole derived by hydrolysis of (I; R = H, R′ = Ph) (cf. Harley-Mason and Bu'Lock, *Biochem. J.*, 1952, **51**, 430); Majima and Kotake's analytical data are more in accord with this formulation (Found: N, 10·1; Cl, 12·3. Calc. for $C_{17}H_{13}N_2Cl$: N, 10·1; Cl, 12·6%).

Urorosein perchlorate can be very conveniently prepared in practically quantitative yield by the addition of perchloric acid to an equimolar mixture of 3-formylindole and indole in methanol. The mechanism of this reaction, which is catalysed by acid, must involve electrophilic substitution of the indole molecule at the reactive position 3 by protonated 3-formylindole (IV).

When pyrrole is treated with one mol. of $POCl_3$ in excess of dimethylformamide, an

83% yield of 2-formylpyrrole can be isolated. This represents a considerable improvement on the original method (Bamberger and Djierdjian, *Ber.*, 1900, **33**, 536) and on the reaction between pyrrylmagnesium halide and formic ester, which gave 35—40% yields (cf. Potokhin, *J. Russ. Phys. Chem. Soc.*, 1927, **59**, 76).

That the mechanism of this reaction is the same as that of the formylation of indole is demonstrated by the absorption spectrum of the reaction mixture in water (Fig. 4, curve *a*) which is very similar to that of 2-methyliminomethylpyrrole hydrochloride (Fig. 4, curve *b*) and therefore almost certainly contains the cation (V). 2-Methyliminoethylpyrrole

FIG. 1. FIG. 2.

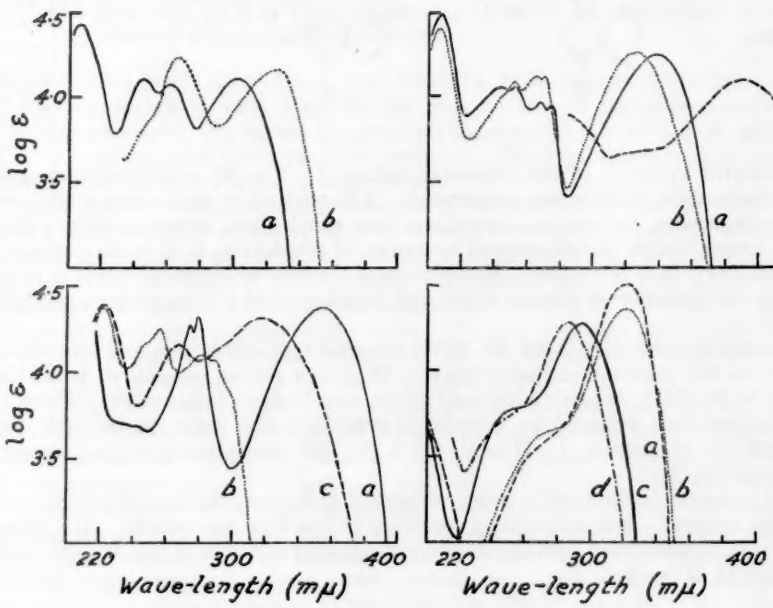


FIG. 3. FIG. 4.

FIG. 1. *a, 3-Formylindole in water; b, in aqueous alkali.*

FIG. 2. *a, 3-Dimethylaminomethyleneindolenine* (II) *hydrochloride in water; b, 3-methyliminomethylindole hydrochloride in water; c,* (I; R = H, R′ = Ph) *hydrochloride in dioxan.*

FIG. 3. *a, 3-Dimethylaminomethyleneindolenine* (II) *in ether; b, 3-methyliminomethylindole in ether; c, 3-phenyliminomethylindole in ether.*

FIG. 4. *a, 2-Dimethylaminomethyleneisopyrrole hydrochloride in water; b, 2-methyliminomethylpyrrole hydrochloride in water; c, 2-formylpyrrole in water; d, 2-methyliminomethylpyrrole in* 95% *ethanol.*

was prepared by Emmert, Diehl, and Gollwitzer (*Ber.*, 1929, **62**, 1737) by the action of methylamine on 2-formylpyrrole. Attempts to isolate 2-dimethylaminomethylenepyrrolenine have so far failed. Methylation of 2-methyliminomethylpyrrole failed to yield a homogeneous product.

EXPERIMENTAL

3-Formylindole.—Phosphorus oxychloride (5·0 c.c., 0·055 mol.; freshly distilled) was added dropwise with stirring to dimethylformamide (16 g., 0·22 mol.) in a flask protected from atmospheric moisture, the temperature being kept at 10—20°. Indole (5·85 g., 0·050 mol.) in dimethylformamide (4 g.) was then slowly added with stirring, the temperature of the mixture being kept at 20—30°. The mixture was kept at 35° for 45 min., then poured on crushed ice, and the clear solution treated at 20—30° with sodium hydroxide (9·5 g., 0·24 mol.) in water (50 c.c.), at such a rate that the solution was always acidic, until about three-

quarters of the alkali had been added. The last quarter was added all at once, and the solution quickly boiled for 1 min. The white crystals were filtered off, carefully washed with water (5 × 25 c.c.), and dried to a constant weight at 100°/10 mm. The off-white product (6·93 g., 95·5%) had m. p. 197—199°.

3-Dimethylaminomethyleneindolenine.—The pale red aqueous reaction mixture, obtained as above (half quantities), was cooled to −5° and very slowly, with efficient stirring, treated with aqueous sodium hydroxide (1·3 equiv.) at −5°. The still acidic solution was left at about 10° for 1 hr., then more alkali (1·6 equiv.) slowly added with stirring at −5°. The weakly acidic solution was well shaken with pre-cooled chloroform (75 c.c.), rapidly treated with pre-cooled aqueous sodium hydroxide (1·15 equiv.), and the whole shaken for 20 sec. The chloroform layer was run on to anhydrous sodium sulphate and then filtered and the chloroform evaporated under reduced pressure. The residue deposited the crystalline *base*, which was filtered off, washed with a little dimethylformamide, and immediately dried at 37°/0·01 mm. The pale yellow plates (2·74 g., 63%) had m. p. 152—154° (Found: C, 76·45; H, 6·3; N, 16·7. $C_{11}H_{12}N_2$ requires C, 76·75; H, 6·95; N, 16·25%).

The *hydrochloride*, prepared by the addition of dry ethereal hydrogen chloride to a solution of the base in chloroform, formed thick prisms, m. p. 224—226° (from ethanol) (Found: Cl, 16·85. $C_{11}H_{12}N_2$,HCl requires Cl, 17·0%).

Hydrolysis. (*a*) The absorption spectrum of the base in water was identical with that of 3-formylindole (Fig. 1, curve *a*). (*b*) The base (133 mg.) was suspended in water (150 c.c.), and 60 c.c. of the water distilled off during 1 hr. The distillate required 7·60 c.c of 0·1N-hydrochloric acid for neutralisation (to pH ~6·5) (Calc. for 3-dimethylaminomethylene-indolenine: 7·74 c.c.). The cooled distillation residue yielded 3-formylindole (109 mg., 97%).

Reduction. The base (340 mg.) was dissolved in boiling ether (100 c.c.) and excess of an ether solution of lithium aluminium hydride added. After 10 min. the mixture was extracted with dilute sulphuric acid, and the aqueous phase filtered, basified, and extracted with ether. The ether extract yielded impure gramine (210 mg.), m. p. 120—127°. A further partition between ether and acid, followed by several crystallisations from aqueous alcohol, yielded a purer product as characteristic leaflets, m. p. 125—130° undepressed by authentic gramine, m. p. 128—132°.

Reaction of 3-Formylindole with Aqueous Methylamine.—3-Formylindole (1·45 g.) was treated with 33% aqueous methylamine (10 c.c.; excess), and the mixture warmed with swirling to 30—35°. After 3 hr. at room temperature, the mixture was extracted with benzene (30 c.c.), the extract dried as far as possible over anhydrous sodium sulphate, and the solvent and the last traces of methylamine and water removed under reduced pressure. The residue (1·60 g.) was a pale brown gum, very soluble in all organic solvents except light petroleum. The *hydrochloride* was prepared by passing dry hydrogen chloride into a dry ether solution of the base. It crystallised from ethanol as pale yellow platelets, m. p. 240—242° (with sublimation), and was extremely soluble in water (Found: Cl, 17·9. $C_{10}H_{10}N_2$,HCl requires Cl, 18·2%).

Ururosein Perchlorate.—A solution of 3-formylindole (1·45 g., 0·01 mole) and indole (1·17 g., 0·01 mole) in hot methanol (15 c.c.) was treated with 60% aqueous perchloric acid (1·7 g., 0·01 mole). Immediate crystallisation occurred giving deep red crystals with a greenish metallic lustre (3·05 g.), which carbonise when heated. The mother-liquor yielded more product (0·22 g.); total yield, 94·5% of theory. The absorption spectrum of the product in alcoholic perchloric acid agreed with that observed for ururosein perchlorate by Harley-Mason and Bu'Lock (*loc. cit.*).

2-Formylpyrrole.—Pyrrole (3·38 g., 0·05 mole) was added slowly with stirring and exclusion of moisture to a mixture of dimethylformamide (15 g., 0·2 mole) and phosphorus oxychloride (5·0 c.c., 0·055 mole), the temperature being kept between 10° and 15°. After 30 min. at 35°, the reddish viscous mixture was poured on ice (30 g.), and the clear solution extracted with ether (100 c.c.). This removed a colourless liquid (0·1 g.) having a strong pyrrole odour. The aqueous phase was treated with sodium hydroxide (10 g., 0·25 mole) in water (20 c.c.), and the alkaline solution left at 15° for 20 min., just acidified with dilute hydrochloric acid and extracted with ether (3 × 75 c.c.). The extracted material was distilled at 8 mm., three fractions being collected: (*a*) b. p. 40—91° (0·81 g.), a mobile liquid; (*b*) b. p. 91—98° (1·79 g.), partially crystalline; and (*c*) b. p. 98—100° (2·62 g.), m. p. 42—44°. Fraction (*b*) was partitioned between water and benzene, and the benzene layer then yielded a product (1·32 g.), m. p. 41—44°. The total yield of 2-formylpyrrole is thus 3·94 g. (83% of theory).

The absorption spectrum of 2-formylpyrrole in water (Fig. 4, curve *c*) is not changed by

the addition of three drops of dilute sodium hydroxide. This is in marked contrast with 3-formylindole, which is thus much more strongly acidic in character.

Reaction of 3-Formylindole with Aniline.—A solution of 3-formylindole (1·45 g.) in pure aniline (5 c.c.; excess) was boiled for 1 min.; water soon began to separate and was removed by reducing the pressure to 10 mm. for a short time. The residual clear solution was kept at 100° for 2 hr. After as much as possible of the excess of aniline had boiled off under reduced pressure, the viscous residue was dissolved in dry ether (10 c.c.), carbon tetrachloride (10 c.c.) was added, and the solid which crystallised out was filtered off; it (1·51 g.) had m. p. 127—129°. The mother liquor was freed from ether and the further crop (0·45 g.) of product filtered off; the total yield of the anil is thus 89%. One crystallisation from dry benzene gave thick prisms, m. p. 128·5—130°.

The hydrochloride was formed in quantitative yield when a dry ethereal solution of the base was treated with a slight excess of dry ethereal hydrogen chloride. The bright yellow salt had m. p. 235—241° (decomp.) (Found: Cl, 13·55. Calc. for $C_{15}H_{12}N_2$,HCl: Cl, 13·8%). This represents an improvement on the material obtained by Majima and Kotake's method (Found: Cl, 13·25, 13·1. Found by Majima and Kotake: Cl, 12·75, 13·1%), which was obviously contaminated with 3-formylindole formed by hydrolysis.

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The Synthesis of Certain Trifluoromethylquinoline Derivatives.

By R. BELCHER, M. STACEY, A. SYKES, and J. C. TATLOW.

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Skraup reactions upon 3-amino-2-, -4-, and -5-nitrobenzotrifluoride afforded 8-nitro-7-, 8-nitro-5-, and 5-nitro-7-trifluoromethylquinoline, respectively, reduction of which gave the corresponding aminotrifluoromethylquinolines. These were deaminated *via* their diazonium salts, and the latter were coupled with β-naphthol and, though the two possessing 8-diazo-groups could not be converted into the 8-hydroxyquinolines, they gave, in the usual way, 8-iodo-7- and -5-trifluoromethylquinoline. 8-Amino-7-trifluoromethylquinoline yielded the 8-hydroxy-analogue when treated with hydrochloric acid. A Skraup reaction on 4-amino-3-hydroxybenzotrifluoride afforded 8-hydroxy-6-trifluoromethylquinoline.

THERE have been several reports of syntheses of trifluoromethylquinolines by Skraup reactions. Gilman and Blume (*J. Amer. Chem. Soc.*, 1943, **65**, 2467) and Pouterman and Girardet (*Experientia*, 1947, **3**, 28) made 5- and 7-trifluoromethylquinoline from 3-aminobenzotrifluoride, and the latter authors (*Helv. Chim. Acta*, 1947, **30**, 107) prepared 6- and 8-trifluoromethylquinoline from the 2- and 4-amino-isomers, whilst Gilman, Tolman, Yeoman, Woods, Shirley, and Avakian (*J. Amer. Chem. Soc.*, 1946, **68**, 426) converted 3-amino-6-nitrobenzotrifluoride into 6-nitro- and thence 6-amino-7-trifluoromethylquinoline. There are three other nitro-3-aminobenzotrifluorides, the 2- and the 4- (Rouche, *Bull. Acad. roy. Belg.*, 1927, **13**, 346; Pouterman and Girardet, *loc. cit.*), and the 5- (Finger and Reed, *J. Amer. Chem. Soc.*, 1944, **66**, 1972) nitro-isomer. This paper reports the application of the Skraup reaction to these compounds, and to 3-amino-4-hydroxybenzotrifluoride, together with investigations on the products and on related trifluoromethylquinoline derivatives, particularly the amines.

Treatment of 3-amino-2-, -4-, and -5-nitrobenzotrifluoride with glycerol, sulphuric acid, and arsenic pentoxide under the conditions recommended by Smith and Richter [" Phenanthroline and Substituted Phenanthroline Indicators," G. F. Smith Chemical Co., Columbus (Ohio), 1944, p. 8; *J. Amer. Chem. Soc.*, 1944, **66**, 396] afforded 8-nitro-7-, 8-nitro-5-, and, as was shown later, 5-nitro-7-trifluoromethylquinoline, respectively. Earlier ideas (Manske, *Chem. Reviews*, 1942, **30**, 113), about the directing effects which applied when Skraup

reactions were carried out upon anilines in which a substituent was in a position *meta* to the amino-group, were as follows: when an *ortho-para*-directing substituent was in the *meta*-position, ring closure occurred on either side of the amino-group whilst, when a *meta*-directing substituent was present, closure was effected between it and the amino-group. More recently, Bradford, Elliott, and Rowe (*J.*, 1947, 437) showed that, at least under the reaction conditions given in the I. G. Farben A.-G. Patent, B.P. 394,416, from *meta*-substituted anilines with (*a*) strongly *ortho-para*-directing groups, 7-substituted quinolines were obtained, with (*b*) weakly *ortho-para*-directing groups, mixtures of 5- and 7-substituted quinolines, the latter isomers predominating, were formed, and with (*c*) *meta*-directing groups, similar mixtures, but with the former isomers predominating, resulted. Hence, if it is assumed that the type of product obtained in a Skraup reaction is not greatly influenced by the reaction conditions, the trifluoromethyl group seems to occupy an anomalous position. Thus, 3-aminobenzotrifluoride gave 5- (6%) and 7- (32%) trifluoromethylquinoline (Gilman and Blume, *loc. cit.*; these figures were essentially confirmed in the present work); 3-amino-6-nitrobenzotrifluoride afforded 6-nitro-7-trifluoromethylquinoline (Gilman, Tolman, *et al.*, *loc. cit.*), and, in this work, from 3-amino-5-nitrobenzotrifluoride only 5-nitro-7-trifluoromethylquinoline was isolated. Thus, the formation of 7-trifluoromethylquinolines seems to be favoured. Though it is, in general, a *meta*-directing substituent, the trifluoromethyl group behaves, in the Skraup synthesis, as would be expected of an *ortho-para*-directing residue. If this effect is due only to variations in reaction conditions between different series, then the classification of directive influences in this particular process would appear to be very difficult. The reason for the discrepancies may lie in steric effects, but it seems unlikely that the trifluoromethyl group is sufficiently large for these to be the only factors involved.

8-Amino-7-trifluoromethylquinoline was obtained by reduction of the nitro-analogue. It was diazotised and the diazo-solution subjected to several standard reactions. Treatment with hypophosphorous acid gave 7-trifluoromethylquinoline, confirming the structure of the amine, and a coupling product was obtained with alkaline β-naphthol. However, the diazo-solution did not give the corresponding 8-hydroxyquinoline, though various reaction conditions were tried. In general, unidentified high-melting resins were obtained. Diazotised 8-amino-5-trifluoromethylquinoline also could not be converted into the hydroxyquinoline (see p. 3850). This failure to give phenols *via* the diazonium salts is apparently common with 8-aminoquinolines, though there are few indications of it in the literature. 8-Iodo-7-trifluoromethylquinoline was made readily from the analogous amine by using the diazo-reaction. With ethanolic or methanolic potassium hydroxide this iodo-derivative gave 7-trifluoromethylquinoline, presumably by a reductive process. This suggested again that substituents in position 8 in this quinoline have some unusual properties.

8-Amino-7-trifluoromethylquinoline would not undergo hydrolysis to the corresponding 7-carboxylic acid with concentrated sulphuric acid. With concentrated hydrochloric acid, however, which effects hydrolysis of the amino-groups of 5- and 7-aminoquinoline (Claus and Howitz, *J. pr. Chem.*, 1893, **47**, 426; Claus and Massau, *ibid.*, **48**, 170; Kochańska and Bobrański, *Ber.*, 1936, **69**, 1807), the amino-group was removed, and but little attack on the trifluoromethyl group occurred, 8-hydroxy-7-trifluoromethylquinoline being formed. The trifluoromethyl group of this compound was hydrolysed with concentrated sulphuric acid, and, after reaction with alcohol, there was obtained ethyl 8-hydroxyquinoline-7-carboxylate, identical with a specimen prepared by carboxylation, etc., of the sodium derivative of 8-hydroxyquinoline.

Diazotisation of 8-amino-5-trifluoromethylquinoline in aqueous sulphuric acid was complicated in that a precipitate was formed, and very little diazonium salt remained in the solution. The structure of this precipitate was not established. By diazotisation of the amine in a solution containing hypophosphorous acid, 5-trifluoromethylquinoline was obtained, confirming the structure of the parent compound. The diazotisation of this amine was best effected by Hodgson and Walker's method using nitrosylsulphuric acid (*J.*, 1933, 1620); dilution with water caused precipitation of the solid mentioned previously, but addition of alkaline β-naphthol gave the corresponding coupling derivative, and aqueous potassium iodide yielded 8-iodo-5-trifluoromethylquinoline. This was converted, by

methanolic sodium methoxide, into 8-methoxy-5-trifluoromethylquinoline, identical with that prepared from 4-chloro-3-nitrobenzotrifluoride (Pettit and Tatlow, following paper). 8-Amino-5-trifluoromethylquinoline was attacked by concentrated sulphuric acid to give what was probably the corresponding amino-carboxylic acid, but which decomposed at the melting point with the formation of 8-aminoquinoline. 8-Amino-5-trifluoromethylquinoline did not give the hydroxy-analogue with concentrated hydrochloric acid, because of preferential attack on the trifluoromethyl group with liberation of fluoride ion; it appeared that this occurred at temperatures below those necessary to remove the amino-group. Application of the Skraup reaction to 8-amino-5-trifluoromethylquinoline did not give a trifluoromethylphenanthroline, again because of attack on the fluoroalkyl group. The only product isolated was 1 : 10-phenanthroline, the trifluoromethyl group being lost, presumably, by hydrolysis to the carboxylic acid, followed by decarboxylation.

3-Amino-4-nitrobenzotrifluoride, by a diazo-reaction gave 3-hydroxy-4-nitrobenzotrifluoride, obtained by De Brouwer (*Bull. Soc. chim. Belg.*, 1930, **39**, 298) by alkaline hydrolysis of the nitro-amine. This nitro-phenol was reduced catalytically to the corresponding amino-phenol, which was stable to dilute acids but lost fluoride ion in warm dilute alkali and gave an amorphous solid product. This effect is similar to that observed with 4-aminobenzotrifluoride itself (Jones, *J. Amer. Chem. Soc.*, 1947, **69**, 2346). 4-Amino-3-hydroxybenzotrifluoride in the Skraup reaction afforded 8-hydroxy-6-trifluoromethylquinoline, which was hydrolysed to the known 8-hydroxyquinoline-6-carboxylic acid.

From 3-amino-5-nitrobenzotrifluoride, a Skraup reaction gave only 5-nitro-7-trifluoromethylquinoline, identified by reduction and deamination to 7-trifluoromethylquinoline, in good yield.

Experimental

3-Amino-5-nitrobenzotrifluoride.—This was made by a slight modification of Finger and Reed's method (*loc. cit.*) by nitration of 3-nitrobenzotrifluoride (114 g.) with nitric acid (200 c.c.) and sulphuric acid (600 c.c.), at 90—100° for 2 hr. and at 120° for 4½ hr., followed by isolation of 3 : 5-dinitrobenzotrifluoride (yield 45%), and partial reduction as described by these authors.

Skraup Reaction on 3-Aminobenzotrifluoride.—The amine (32·2 g.), glycerol (73·6 g.), and arsenic pentoxide (34·5 g.) were stirred mechanically, whilst concentrated sulphuric acid (40·0 g.) was added slowly. The mixture was heated to 135° and after 1 hr. it was refluxed for a further 3 hr. After isolation by Gilman and Blume's method (*loc. cit.*), there were obtained 7- (12·4 g.), m. p. 67°, and 5-trifluoromethylquinoline (3·5 g.), b. p. 214—217°. The only product obtained from the reaction of 7-trifluoromethylquinoline with fuming nitric acid–sulphuric acid was *7-trifluoromethylquinolinium nitrate*, m. p. 171° (Found: C, 46·2; H, 2·6; F, 21·4. $C_{10}H_7O_3N_2F_3$ requires C, 46·15; H, 2·7; F, 21·9%), from which, by treatment with aqueous ammonia, the original quinoline was regenerated.

From attempts to nitrate 5-trifluoromethylquinoline only the starting material was obtained.

8-Nitro-7-trifluoromethylquinoline.—3-Amino-2-nitrobenzotrifluoride (20·6 g.), glycerol (36·8 g.; dried at 180° for 2 hr.), and arsenic pentoxide (17·2 g.) were stirred, and sulphuric acid (17 g.) was added slowly. The mixture was heated cautiously for 1 hr. (at *ca.* 135°) so that the ensuing reaction never became vigorous, and finally it was refluxed for a further 3 hr., stirring being continued throughout. The mixture was poured into water and neutralised with aqueous sodium hydroxide (2N); the precipitate was removed and treated with charcoal in boiling ethyl alcohol, and the solution filtered and concentrated. The deposited solid afforded *8-nitro-7-trifluoromethylquinoline* (3·4 g.), m. p. 167° (from ethyl alcohol) (Found: C, 49·5; H, 1·9; F, 23·3. $C_{10}H_5O_2N_2F_3$ requires C, 49·6; H, 2·1; F, 23·5%).

8-Amino-7-trifluoromethylquinoline.—The nitro-compound (4·75 g.), concentrated hydrochloric acid (50 c.c.), and stannous chloride dihydrate (30 g.) were heated under reflux for 30 min. and then cooled. The precipitate was filtered off and treated with aqueous sodium hydroxide until the solution was strongly alkaline, and the suspension extracted with ether. The extracts were washed, dried ($MgSO_4$), filtered, and evaporated, and the residue was crystallised from aqueous ethyl alcohol to give *8-amino-7-trifluoromethylquinoline* (3·40 g.), m. p. 156° (Found: C, 56·6; H, 3·1; F, 26·4. $C_{10}H_7N_2F_3$ requires C, 56·6; H, 3·3; F, 26·9%). This amine was unattacked after 3 hr. with concentrated sulphuric acid at 200°; after 3 hr. at 220° charring had occurred and no product could be isolated.

The N-*acetyl* derivative (from ethyl alcohol) had m. p. 200·5—201° (Found : C, 56·6; H, 3·2; F, 22·2. $C_{12}H_9ON_2F_3$ requires C, 56·7; H, 3·6; F, 22·4%).

Diazotisation of 8-*Amino*-7-*trifluoromethylquinoline*.—This amine (0·50 g.), in water (20 c.c.) and concentrated hydrochloric acid (1·25 c.c.) at 0°, was diazotised by addition of sodium nitrite (0·17 g.) in water (2·5 c.c.), and, after 15 min., urea was added. The solution was divided into two equal parts; to one was added hypophosphorous acid (3·0 c.c. of 30%), and after 16 hr. at 15°, the solution was made alkaline with sodium hydroxide; the resultant precipitate gave 7-trifluoromethylquinoline (0·15 g.), m. p. and mixed m. p. 67° (from aqueous ethyl alcohol) (Found : C, 60·7; H, 3·3. Calc. for $C_{10}H_6NF_3$: C, 60·9; H, 3·1%).

To the second portion of the diazo-solution β-naphthol in alkali was added. Recrystallisation of the red precipitate from acetic acid afforded 7-*trifluoromethyl*-8-*quinolylazo*-β-*naphthol* (0·41 g.), m. p. 233° (Found : C, 65·4; H, 3·3; F, 15·6. $C_{20}H_{12}ON_3F_3$ requires C, 65·4; H, 3·3; F, 15·5%).

8-*Iodo*-7-*trifluoromethylquinoline*.—8-Amino-7-trifluoromethylquinoline (1·00 g.) was diazotised at 5° by means of sulphuric acid (6 c.c.; 6N) and sodium nitrite (0·36 g.) in water (5 c.c.). A little urea was added, and then the solution was added to water (5 c.c.) containing potassium iodide (1·0 g.). After 2 hr. at 15° the precipitate was filtered off and recrystallised from aqueous ethyl alcohol to give 8-*iodo*-7-*trifluoromethylquinoline* (0·67 g.), m. p. 112° (Found : C, 37·5; H, 1·6; I, 39·2; F, 17·3. $C_{10}H_5NIF_3$ requires C, 37·2; H, 1·6; I, 39·3; F, 17·6%).

Action of Alcoholic Potassium Hydroxide on 8-*Iodo*-7-*trifluoromethylquinoline*.—The iodo-compound (2·0 g.) was refluxed in ethanolic potassium hydroxide (35%; 10 c.c.) for 6 hr. The solution was diluted with an excess of water and the precipitate was filtered off and distilled (at 15 mm.) on to a cold finger to give 7-trifluoromethylquinoline (0·65 g.), m. p. and mixed m. p. 66—67° (Found : C, 61·1; H, 3·0%). A similar experiment in which the iodo-compound (1·00 g.) was refluxed for 5 hr. with potassium hydroxide (4·0 g.) in methyl alcohol (7·0 c.c.) and water (3·0 c.c.) gave the same product (0·36 g.), m. p. and mixed m. p. 66—67°.

8-*Hydroxy*-7-*trifluoromethylquinoline*.—8-Amino-7-trifluoromethylquinoline (1·00 g.) and concentrated hydrochloric acid (20·0 c.c.) were heated in a sealed tube at 220° ± 5° for 4 hr. The solution was filtered, made alkaline with ammonia solution (*d* 0·88), and then neutralised with glacial acetic acid. The precipitate was filtered off, and recrystallised from ethyl alcohol to give 8-*hydroxy*-7-*trifluoromethylquinoline* (0·341 g.), m. p. 252° (Found : C, 56·2; H, 2·7; F, 26·8%; *M*, 225. $C_{10}H_6ONF_3$ requires C, 56·3; H, 2·8; F, 26·7%; *M*, 213). The O-*toluene*-p-*sulphonate* (52%; from aqueous ethyl alcohol) had m. p. 114° (Found : C, 55·9; H, 3·2; F, 15·2. $C_{17}H_{12}O_3NSF_3$ requires C, 55·6; H, 3·3; F, 15·5%), and the O-p-*nitrobenzoate* (49%; from aqueous ethyl alcohol), m. p. 157—158° (Found : C, 56·7; H, 2·7. $C_{17}H_9O_4N_2F_3$ requires C, 56·4; H, 2·5%).

Treatment of the hydroxy-compound for 3 hr. at 15° with ethereal diazomethane afforded 8-*methoxy*-7-*trifluoromethylquinoline* (60%), m. p. 79° (from aqueous ethyl alcohol) (Found : C, 58·5; H, 3·6. $C_{11}H_8ONF_3$ requires C, 58·15; H, 3·55%).

Ethyl 8-*Hydroxyquinoline*-7-*carboxylate*.—8-Hydroxy-7-trifluoromethylquinoline (0·050 g.) was heated with concentrated sulphuric acid (1·0 c.c.) for 90 min. at 180—190°. The solution was cooled, ethyl alcohol (3·0 c.c.) was added, and after 4 hours' refluxing the whole was neutralised carefully with sodium hydrogen carbonate. After 16 hr., crystals had separated; recrystallisation from benzene–light petroleum (b. p. 60—80°) afforded ethyl 8-hydroxyquinoline-7-carboxylate (0·034 g.), m. p. 88° (Found : C, 66·3; H, 5·3. Calc. for $C_{12}H_{11}O_3N$: C, 66·3; H, 5·1%) undepressed on admixture with a specimen prepared by Einhorn and Pfyl's method (*Annalen*, 1900, **311**, 26).

8-*Nitro*-5-*trifluoromethylquinoline*.—3-Amino-4-nitrobenzotrifluoride, when treated with glycerol, arsenic pentoxide, and sulphuric acid as described for its isomer, the mixture being refluxed for 4 hours, afforded 8-*nitro*-5-*trifluoromethylquinoline* (26%), m. p. 74—75° (Found : C, 49·4; H, 1·8; F, 23·7%).

Reduction of 8-*Nitro*-5-*trifluoromethylquinoline*.—Carried out as described for the 7-trifluoromethyl isomer, this reaction gave 8-*amino*-5-*trifluoromethylquinoline* (56%), m. p. 89° (after recrystallisation from ethyl alcohol, unchanged by sublimation *in vacuo*) (Found : C, 56·9; H, 3·3; F, 26·6%). Its *acetyl* derivative had m. p. 114° (from aqueous ethyl alcohol) (Found : C, 56·5; H, 3·4%).

Action of Acids on 8-*Amino*-5-*trifluoromethylquinoline*.—(a) *Sulphuric acid*. The amine (0·20 g.) and concentrated sulphuric acid (2·0 c.c.) were heated for 90 min. at 160°. Partial neutralisation with ammonia solution (2N) caused precipitation from the solution (*A*) of a yellow solid. This was filtered off and dissolved in aqueous sodium hydroxide; addition of hydrochloric acid (to pH 7) precipitated (probably) the 8-amino-5-carboxylic acid, m. p. 242° (decomp.). At

this temperature it gave 8-aminoquinoline (0·027 g.), m. p. and mixed m. p. 63—64°. Complete neutralisation of solution (*A*) with ammonia solution gave 8-amino-5-trifluoromethylquinoline (0·05 g.), m. p. and mixed m. p. 89°.

(b) *Hydrochloric acid.* The amine was unattacked by concentrated hydrochloric acid at 75° for 6 hr. At 90° and at 110° a compound, m. p. 62—63°, probably 8-aminoquinoline, was isolated in very small yield (*ca.* 1%), fluoride ion being present in the aqueous phase. At 200°, fluoride ion was removed and no identifiable product was found.

5-Trifluoromethylquinoline.—8-Amino-5-trifluoromethylquinoline (0·75 g.) in sulphuric acid (18 c.c.; 6N) was diazotised at 5° with sodium nitrite (0·30 g.) in water (5 c.c.). A precipitate was formed immediately, and was filtered off, washed, and recrystallised from ethyl alcohol to give a substance (0·60 g.), m. p. 161° [Found: C, 49·0; H, 2·3; F, 23·7%; *M* (Rast), 225].

In a second experiment, sodium nitrite (0·18 g.), in water (2·5 c.c.), was added to a mixture of the amine (0·50 g.), water (10 c.c.), concentrated sulphuric acid (1·0 c.c.), and hypophosphorous acid (3·0 c.c.; 30%), at 0°. After 16 hr. at 15°, the solution was filtered, made alkaline with sodium hydroxide, and extracted with ether. The extracts were washed, dried ($MgSO_4$), filtered, and evaporated. The liquid residue, in ethyl alcohol, was treated with saturated alcoholic picric acid. The yellow precipitate, after recrystallisation from ethyl alcohol, gave *5-trifluoromethylquinolinium picrate* (10%), m. p. and mixed m. p. 185° (Found: C, 45·2; H, 1·8. $C_{16}H_9O_7N_4F_3$ requires C, 45·1; H, 2·1%).

Diazotisation of 8-Amino-5-trifluoromethylquinoline by Means of Nitrosylsulphuric Acid.—Sodium nitrite (0·48 g.) was added slowly to concentrated sulphuric acid (4·8 c.c.) at 70°. The solution was cooled, and the amine (0·65 g.), in glacial acetic acid (2·3 c.c.), was added so that the temperature did not rise above 30°. The solution was divided into two portions. To one was added an excess of ice–water; the precipitated substance, after recrystallisation from ethyl alcohol, had m. p. and mixed m. p. with above product 161°. Alkaline β-naphthol was added to the second portion of the diazo-solution, and the red precipitate was recrystallised from acetone to give *5-trifluoromethyl-8-quinolylazo-β-naphthol* (64%), m. p. 240° (Found: C, 65·0; H, 3·1. $C_{20}H_{12}ON_3F_3$ requires C, 65·4; H, 3·3%).

8-Iodo-5-trifluoromethylquinoline.—The amine (0·65 g.) was diazotised with nitrosylsulphuric acid, as above, and the solution was added at 0° to water (5 c.c.) containing potassium iodide (0·7 g.). After 2 hr. at 15° the precipitate was filtered off, recrystallised from ethyl alcohol, and then sublimed, to give *8-iodo-5-trifluoromethylquinoline* (0·29 g.), m. p. 62—63° (Found: C, 37·0; H, 1·3. $C_{10}H_5NIF_3$ requires C, 37·2; H, 1·6%).

8-Methoxy-5-trifluoromethylquinoline.—The 8-iodo-compound (0·30 g.) was refluxed for 6 hr. in dry methyl alcohol (2·0 c.c.) containing sodium methoxide [from sodium (0·2 g.)]. The solution was cooled, excess of water added, and the precipitate filtered off, washed, dried, and recrystallised from light petroleum (b. p. 60—80°) to give 8-methoxy-5-trifluoromethylquinoline (0·09 g.), m. p. 80—81°, not depressed on admixture with the specimen described by Pettit and Tatlow (*loc. cit.*) (Found: C, 58·4; H, 3·6. Calc. for $C_{11}H_8ONF_3$: C, 58·15; H, 3·55%).

Skraup Reaction on 8-Amino-5-trifluoromethylquinoline.—The quinoline (2·12 g.), glycerol (3·68 g.), arsenic pentoxide (1·79 g.), and concentrated sulphuric acid (1·9 g.) were stirred and heated at 135° for 1 hr. and then refluxed (bath temp. 160—170°) for 1½ hr. After being poured into water the mixture was made alkaline with ammonia solution, and the resultant precipitate filtered off and extracted with hot benzene. The extracts were concentrated; the solid which was deposited was recrystallised from benzene–light petroleum (b. p. 60—80°) to give 1 : 10-phenanthroline monohydrate (0·51 g.), m. p. and mixed m. p. 93—94° (Found: C, 72·0; H, 5·2. Calc. for $C_{12}H_8N_2,H_2O$: C, 72·7; H, 5·1%). After 3 hr. at 50°/15 mm. over phosphoric oxide, the product, then anhydrous, had m. p. 117°. Smith and Richter (*op. cit.*) gave m. p. 117° (anhydrous) and m. p. 99—100° (monohydrate).

From a similar reaction at 135° for 2 hr. the same product was isolated.

3-Hydroxy-4-nitrobenzotrifluoride—3-Amino-4-nitrobenzotrifluoride was diazotised and the product treated with copper sulphate as described by Whalley (*J.*, 1949, 3016) for the 3-amino-5-nitro-isomer (the product was steam-distilled from the mixture). 3-Hydroxy-4-nitrobenzotrifluoride (73%), b. p. 108—111°/34 mm., was obtained. It gave a *p*-nitrobenzoate, m. p. 106° (from ethyl alcohol) (Found: C, 47·2; H, 2·3. Calc. for $C_{14}H_7O_6N_2F_3$: C, 47·2; H, 2·0%). Whalley (*J.*, 1950, 2792) gave m. p. 103° for this ester.

4-Amino-3-hydroxybenzotrifluoride.—3-Hydroxy-4-nitrobenzotrifluoride (14·0 g.), ethyl alcohol (150 c.c.), and Raney nickel (*ca.* 1·5 g.) were shaken at *ca.* 20°/1 atm. in hydrogen until absorption was complete. The solution was filtered and evaporated *in vacuo*. The residue was recrystallised from benzene to give *4-amino-3-hydroxybenzotrifluoride* (8·8 g.), m. p. 114—115°

(Found : C, 47·4; H, 3·4; F, 32·5. $C_7H_6ONF_3$ requires C, 47·5; H, 3·4; F, 32·2%). When the hydroxy-amine was heated to 117°, or over, the liquid re-solidified, apparently with evolution of hydrogen fluoride. The *diacetyl* derivative (acetic anhydride–acetic acid) (58%, from aqueous ethyl alcohol), m. p. 113° (Found : C, 50·7; H, 3·6; F, 21·4. $C_{11}H_{10}O_3NF_3$ requires C, 50·6; H, 3·9; F, 21·8%), was soluble in dilute aqueous sodium hydroxide and was recovered by acidification. Use of less acetic anhydride afforded a *monoacetyl* derivative (57%; from aqueous ethyl alcohol), m. p. 199° (Found : C, 49·6; H, 3·8; F, 25·8. $C_9H_8O_2NF_3$ requires C, 49·3; H, 3·7; F, 26·0%).

The hydroxy-amine was soluble in dilute hydrochloric acid and could be recovered, even after the solution had been heated, by neutralisation with ammonia solution. A solution of the compound in dilute aqueous sodium hydroxide, however, when warmed, deposited a white amorphous organic precipitate, m. p. >350°. Fluoride ion appeared in the solution.

8-Hydroxy-6-trifluoromethylquinoline.—4-Amino-3-hydroxybenzotrifluoride (6·6 g.), glycerol (13·8 g.), arsenic pentoxide (6·4 g.), and concentrated sulphuric acid (6·9 g.) were stirred and heated at 135° for 1 hr. and then under reflux for 1½ hr. The mixture was poured into water, the solution made alkaline with ammonia solution, and the pH adjusted to 6—7 with acetic acid. The resultant precipitate was filtered off, washed, recrystallised from aqueous ethyl alcohol (charcoal), and sublimed at 15 mm. to give *8-hydroxy-6-trifluoromethylquinoline* (2·8 g.), m. p. 95° (Found : C, 56·6; H, 3·1; F, 27·2%; *M*, 215. $C_{10}H_6ONF_3$ requires C, 56·3; H, 2·8; F, 26·7%; *M*, 213). The *toluene*-p-*sulphonyl* ester (61%) had m. p. 179·5° (Found : C, 55·8; H, 3·3; F, 15·6%), and the p-*nitrobenzyl ester* (53%; from aqueous acetone) m. p. 150° (Found : C, 56·3; H, 2·6; F, 15·5. $C_{17}H_9O_4N_2F_3$ requires C, 56·4; H, 2·5; F, 15·7%).

8-Hydroxyquinoline-6-carboxylic Acid.—8-Hydroxy-6-trifluoromethylquinoline (0·150 g.) and concentrated sulphuric acid (1·0 c.c.) were stirred at 160—170° for 30 min. After being made alkaline with dilute aqueous sodium hydroxide, the solution was neutralised with dilute hydrochloric acid. The resultant precipitate was crystallised from ethyl alcohol to give 8-hydroxyquinoline-6-carboxylic acid (0·097 g.), m. p. 286—288° (Found : C, 63·7; H, 3·9; N, 7·5. Calc. for $C_{10}H_7O_3N$: C, 63·5; H, 3·7; N, 7·4%), for which Niementowski and Sucharda (*Ber.*, 1916, **49**, 12) gave m. p. 284°.

5-Nitro- and 5-Amino-7-trifluoromethylquinoline.—3-Amino-5-nitrobenzotrifluoride, treated as for the 3-amino-2-nitro-isomer gave, after recrystallisation from carbon tetrachloride, *5-nitro-7-trifluoromethylquinoline* (15%), m. p. 99° (Found : C, 49·6; H, 2·2; F, 23·3%). Reduction of this product, by the method previously described, afforded *5-amino-7-trifluoromethylquinoline* (91%), m. p. 145—145·5° (Found : C, 56·7; H, 3·0%).

This amine (0·30 g.) was diazotised in the usual way. To two-thirds of the resulting solution was added hypophosphorous acid (3·0 c.c.; 30%), and after 16 hr. at 15° and isolation as before there was obtained 7-trifluoromethylquinoline (0·14 g.), m. p. and mixed m. p. 67°. The remaining one-third of the diazo-solution was treated with alkaline β-naphthol, giving *7-trifluoromethyl-5-quinolylazo-β-naphthol* (86%; from glacial acetic acid), m. p. 240° (Found : C, 65·1; H, 3·1%).

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8-*Hydroxy*-5-*trifluoromethylquinoline.*

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4-Chloro-3-nitrobenzotrifluoride gave, with ammonia, the 4-amino-analogue, from which 4-hydroxy-3-nitro- and thence 3-amino-4-hydroxybenzotrifluoride were made. A Skraup reaction on the latter afforded 8-hydroxy-5-trifluoromethylquinoline. Methylation of this gave the 8-methoxy-derivative, prepared also from 3-amino-4-methoxybenzotrifluoride.

This work is part of an investigation upon the organic and analytical chemistry of trifluoromethylquinoline derivatives (see also Belcher, Stacey, Sykes, and Tatlow, preceding paper; Belcher, Sykes, and Tatlow, *J.*, 1954, in the press), and was directed particularly towards the synthesis of 8-hydroxy-5-trifluoromethylquinoline. 4-Chloro-3-nitrobenzotrifluoride (I.G. Farben. A.-G., F.P. 745,293; *Chem. Abs.*, 1933, **27**, 4414) was used as starting material since it possesses a reactive chlorine atom. A complication which arises, however, is that, when, by exchange of this atom an activating substituent has been introduced into the position *para* to the trifluoromethyl group, the reactivity of the latter may be enhanced considerably, so that its fluorine may be subsequently lost. Thus, when treated with aqueous-alcoholic potassium hydroxide, the 4-chloro-compound afforded 4-hydroxy-3-nitrobenzoic acid, also formed in small yield by the action of sodium carbonate or nitrite, reagents which give the phenol from 1-chloro-2 : 4-dinitrobenzene (Clemm, *J. prakt. Chem.*, 1870, **1**, 145; Kym, *Ber.*, 1901, **34**, 3311). However, with alcoholic ammonia at 120°, the trifluoromethyl group was unattacked and 4-amino-3-nitrobenzotrifluoride was formed (cf. Hoffa and Müller, U.S.P. 2,056,899). With aqueous-alcoholic ammonia at higher temperatures, the yield of amine was greatly reduced, there being obtained also a high-melting solid, formed apparently by intermolecular elimination of hydrogen fluoride.

Diazotisation of the nitro-amine, followed by heating, gave 4-hydroxy-3-nitrobenzotrifluoride which was stable when pure, but was hydrolysed readily by dilute alkali to 4-hydroxy-3-nitrobenzoic acid, and on catalytic hydrogenation afforded 3-amino-4-hydroxybenzotrifluoride. This compound, by a Skraup reaction, afforded 8-hydroxy-5-trifluoromethylquinoline, which, as expected, was unstable in an alkaline medium, the fluorine being liberated readily as fluoride ion. Loss of fluorine occurred even in the cold under the mild conditions (N/20-alkali) used in analytical tests (Belcher, Sykes, and Tatlow, *loc. cit.*). Methylation of the hydroxyquinoline by diazomethane gave 8-methoxy-5-trifluoromethylquinoline, identical with the compound made independently from 8-amino-5-trifluoromethylquinoline (Belcher, Stacey, Sykes, and Tatlow, *loc. cit.*). This 8-methoxy-derivative was prepared also by a Skraup reaction upon 3-amino-4-methoxybenzotrifluoride, which had been made from 4-chloro-3-nitrobenzotrifluoride by Benkeser and Buting's method (*J. Amer. Chem. Soc.*, 1952, **74**, 3011). Catalytic reduction of 4-methoxy-3-nitrobenzotrifluoride afforded not only the amine but in one case also the corresponding azo- and azoxy-compounds.

In contrast to the hydroxy-compound, 8-methoxy-5-trifluoromethylquinoline was not attacked by boiling aqueous-alcoholic alkali. Boiling hydriodic acid demethylated it but, in a Zeisel determination, a reaction time of 8 hr. or so was apparently needed for a quantitative methoxyl recovery. On a larger scale, etching in the reflux condenser suggested that the trifluoromethyl group also had been hydrolysed, presumably after the demethylation. The only material isolated, however, was 8-hydroxyquinoline, the process having gone still further, in that the expected 5-carboxylic acid had suffered decarboxylation. A similar effect was found with the corresponding 8-amino-compound (Belcher, Stacey, Sykes, and Tatlow, *loc. cit.*).

Experimental

Amination of 4-Chloro-3-nitrobenzotrifluoride.—The chloronitro-compound (50·0 g.) and saturated ammoniacal ethyl alcohol (250 c.c.) were heated at 120° in an autoclave under autogenous pressure for 5 hr. The solution was concentrated and the residue was recrystallised from

aqueous ethyl alcohol to give 4-amino-3-nitrobenzotrifluoride (35·5 g.), m. p. 106—107° (Found: C, 41·0; H, 2·5; F, 27·4. Calc. for $C_7H_5O_2N_2F_3$: C, 40·8; H, 2·4; F, 27·7%) (F.P. 745,293 gives m. p. 109—110°). Treatment of the product in ether with trifluoroacetic anhydride yielded the N-*trifluoroacetyl* derivative, m. p. 65—66° (Found: C, 35·7; H, 1·5. $C_9H_4O_3N_2F_6$ requires C, 35·8; H, 1·3%).

The N-*acetyl* derivative, prepared by use of acetic acid–acetic anhydride, had m. p. 112—113° (Found: C, 43·4; H, 2·7. $C_9H_7O_3N_2F_3$ requires C, 43·6; H, 2·8%).

4-*Hydroxy*-3-*nitrobenzotrifluoride*.—4-Amino-3-nitrobenzotrifluoride (15·0 g.) was dissolved in concentrated sulphuric acid (40 c.c.) and water (10 c.c.), and diazotised with a saturated solution of sodium nitrite. The resulting solution was added gradually to a boiling solution of copper sulphate pentahydrate (70 g.) in water (200 c.c.), volatile matter being continuously removed in steam. The distillate was extracted with ether, and the extracts were dried ($MgSO_4$) and evaporated. Distillation of the residue afforded 4-*hydroxy*-3-*nitrobenzotrifluoride* (7·1 g.), a pale yellow oil, b. p. 92—94°/12 mm. (Found: C, 40·6; H, 1·8; F, 27·3. $C_7H_4O_3NF_3$ requires C, 40·6; H, 1·95; F, 27·5%). Its *toluene*-p-*sulphonyl* ester had m. p. 58—59° (Found: C, 46·6; H, 2·5. $C_{14}H_{10}O_5NSF_3$ requires C, 46·5; H, 2·8%).

Hydrolysis of 4-*Hydroxy*-3-*nitrobenzotrifluoride*.—A solution of the nitrophenol (0·42 g.) in ethyl alcohol (2·0 c.c.) was added slowly to an excess of hot aqueous sodium hydroxide (10%). The mixture was heated under gentle reflux for 20 min., cooled, and acidified with concentrated hydrochloric acid. Recrystallisation of the precipitate from water gave 4-hydroxy-3-nitrobenzoic acid (0·28 g.), m. p. 181—182° (Found: C, 45·7; H, 2·7. Calc. for $C_7H_5O_5N$: C, 45·9; H, 2·75%). Biehringer and Borsum (*Ber.*, 1915, **48**, 1314) recorded m. p. 182—183° for this acid.

Action of Potassium Hydroxide on 4-*Chloro*-3-*nitrobenzotrifluoride*.—To a solution of 4-chloro-3-nitrobenzotrifluoride (2·15 g.) in ethyl alcohol (11 c.c.) a solution of potassium hydroxide (3·3 g.) in water (11 c.c.) was added. The mixture was refluxed for 15 hr., filtered, and extracted with ether. The dried extract was evaporated to give an orange liquid (0·11 g.). The yellow aqueous phase was acidified with concentrated hydrochloric acid, a second ether extraction was carried out, and the residue obtained after evaporation of the ether was recrystallised from water to give 4-hydroxy-3-nitrobenzoic acid (1·40 g.), m. p., and mixed m. p. with the material reported above, 181—182°.

Reduction of 4-*Hydroxy*-3-*nitrobenzotrifluoride*.—4-Hydroxy-3-nitrobenzotrifluoride (6·32 g.) in ethyl alcohol (50 c.c.) was reduced by hydrogen–Raney nickel at atmospheric pressure. When the theoretical amount of hydrogen had been absorbed, the dark solution was evaporated to dryness under diminished pressure. The residue was recrystallised from benzene, giving needles of 3-*amino*-4-*hydroxybenzotrifluoride* (4·92 g.), m. p. 121—122° (Found: C, 47·7; H, 3·2. $C_7H_6ONF_3$ requires C, 47·5; H, 3·4%); the *acetyl* derivative had m. p. 157—158° (Found: C, 49·5; H, 3·7. $C_9H_8O_2NF_3$ requires C, 49·3; H, 3·7%).

Skraup Reaction upon 3-*Amino*-4-*hydroxybenzotrifluoride*.—3-Amino-4-hydroxybenzotrifluoride (2·19 g.), arsenic oxide (2·4 g.), glycerol (4·9 g.), and concentrated sulphuric acid (2·9 g.) were stirred and heated at 160—175° for 3½ hr. When cool, the mixture was stirred with water (200 c.c.), and the pH of the solution was brought to 4 by addition of saturated sodium acetate solution. After exhaustive extraction with ether, the extracts were dried (Na_2SO_4) and evaporated, and the residue was recrystallised from ethyl alcohol to give 8-*hydroxy*-5-*trifluoromethylquinoline* (0·70 g.), m. p. 92—96°, which was sublimed *in vacuo* to give a very pale yellow solid, m. p. 96—97°, depressed by the 6-trifluoromethyl isomer (m. p. 95°; Belcher, Stacey, Sykes, and Tatlow, *loc. cit.*) (Found: C, 56·6; H, 2·6; F, 26·7. $C_{10}H_6ONF_3$ requires C, 56·3; H, 2·8; F, 26·7%). The *toluene*-p-*sulphonate* had m. p. 156·5—157·5° (Found: C, 55·8; H, 3·4. $C_{17}H_{12}O_3NSF_3$ requires C, 55·6; H, 3·3%).

Methylation of 8-*Hydroxy*-5-*trifluoromethylquinoline*.—To the trifluoromethylquinolinol (0·073 g.) in dry ether (30 c.c.) was added a solution of diazomethane (*ca.* 0·1 g.) in dry ether (30 c.c.), and the mixture was set aside for 48 hr. It was then filtered and evaporated at 20°/15 mm. The residual solid was taken up in ether, and the solution washed with aqueous sodium hydroxide, dried ($MgSO_4$), and evaporated. Recrystallisation afforded pale yellow prisms of 8-methoxy-5-trifluoromethylquinoline (0·045 g.), m. p. and mixed m. p. 80°, identical with that reported below.

Preparation of 3-*Amino*-4-*methoxybenzotrifluoride*.—4-Methoxy-3-nitrobenzotrifluoride (Benkeser and Buting, *loc. cit.*) (25·0 g.), ethyl alcohol (50 c.c.), and concentrated hydrochloric acid (80 c.c.) were stirred, and stannous chloride dihydrate (100 g.) added portion-wise. The mixture was refluxed for 30 min. and then poured on an excess of aqueous sodium hydroxide and crushed ice. Extraction as usual, followed by recrystallisation from light petroleum (b. p. 60—80°), afforded 3-amino-4-methoxybenzotrifluoride (15·0 g.), m. p. 58—59°. Brown, Suckling, and

Whalley (*J.*, 1949, S 95) recorded m. p. 59°; see also Whalley (*J.*, 1949, 3016). The *trifluoroacetyl* derivative, prepared by the action of trifluoroacetic anhydride on an ethereal solution, had m. p. 99—101° (Found : C, 41·9; H, 2·8. $C_{10}H_7O_2NF_6$ requires C, 41·8; H, 2·5%).

Catalytic reduction of the parent nitro-compound by Benkeser and Buting's method (*loc. cit.*) also gave the amine; from a reduction which was incomplete there were also obtained, by fractional crystallisation from ethyl alcohol, red needles of 2 : 2′-*dimethoxy*-5 : 5′-*bistrifluoromethylazobenzene*, m. p. 215—216° (Found : C, 51·0; N, 2·9. $C_{16}H_{12}O_2N_2F_6$ requires C, 50·8; H, 3·2%), and pale yellow prisms of 2 : 2′-*dimethoxy*-5 : 5′-*bistrifluoromethylazoxybenzene*, m. p. 133° (Found : C, 48·7; H, 3·2. $C_{16}H_{12}O_3N_2F_6$ requires C, 48·7; H, 3·1%).

Preparation of 8-*Methoxy*-5-*trifluoromethylquinoline*.—3-Amino-4-methoxybenzotrifluoride (4·85 g.), glycerol (8·2 g.), arsenic oxide (4·3 g.), and concentrated sulphuric acid (5·0 g.) were stirred and heated at 135° for 1 hr., and then at 160—170° for a further 3 hr. Excess of alkali was added to the product, which was subsequently exhaustively extracted with ether. The extracts were dried ($MgSO_4$) and evaporated. Recrystallisation of the residue first from aqueous ethyl alcohol and then from light petroleum (b. p. 60—80°) yielded 8-*methoxy*-5-*trifluoromethylquinoline* (1·71 g.), m. p. 81—82° undepressed in admixture with the material described by Belcher, Stacey, Sykes, and Tatlow (*loc. cit.*) (Found : C, 57·8; H, 3·9; F, 24·7. $C_{11}H_8ONF_3$ requires C, 58·1; H, 3·55; F, 25·1%). This compound was unattacked when boiled with aqueous-alcoholic potassium hydroxide (5N) for 5 hr. No fluoride ion was detected, the starting material (77%), m. p. and mixed m. p. 80°, being obtained.

Action of Hydriodic Acid on 8-*Methoxy*-5-*trifluoromethylquinoline*.—The quinoline (0·455 g.) was heated under reflux with hydriodic acid (20 c.c.; *d* 1·7) for 25 hr. Etching in the condenser indicated that hydrolysis of the trifluoromethyl group had occurred. The residual liquid was diluted with water (80 c.c.), and the liquid was extracted with ether. A saturated solution of sodium acetate was added (pH then *ca.* 4) and a second extraction with ether was carried out. After being dried (Na_2SO_4), this extract was evaporated, and the residue recrystallised from light petroleum (b. p. 60—80°) to give 8-hydroxyquinoline (0·094 g.), m. p. and mixed m. p. 74—75° (Found : C, 74·0; H, 4·7. Calc. for C_9H_7ON : C, 74·45; H, 4·9%).

The authors thank Professor M. Stacey, F.R.S., for his interest, and Miss D. S. Leather for carrying out the elemental analyses.

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The Synthesis of 4-*Deoxypyridoxine Phosphates.*

By R. F. LONG and A. L. MORRISON.

[Reprint Order No. 5473.]

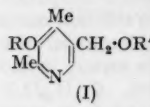
The preparation of the two crystalline dihydrogen phosphates of 4-deoxypyridoxine is described.

EARLY phosphorylations of 4-deoxypyridoxine (I; R = R′ = H) gave products which inhibited dissociated pyridoxal phosphate dependent enzymes (Beiler and Martin, *J. Biol. Chem.*, 1947, **169**, 345; Umbreit and Waddell, *Proc. Soc. Exp. Biol. Med.*, 1949, **70**, 293) but were not specified nor fully described. Recently, pure 4-deoxypyridoxine 5-(dihydrogen phosphate) [I; R = H, R′ = $PO(OH)_2$] has been prepared (Peterson and Sober, *J. Amer. Chem. Soc.*, 1954, **76**, 169). We have prepared this compound in lower yield by a less direct route and also the isomeric 4-deoxypyridoxine 3-(dihydrogen phosphate) [I; R = $PO(OH)_2$, R′ = H].

Reaction of the potassium salt of (I; R = R′ = H) with tetrabenzyl pyrophosphate in *tert.*-butanol (Atherton and Todd, B.P. 674,089) gave dibenzyl 5-hydroxymethyl-2 : 4-dimethyl-3-pyridyl phosphate [I; R = $PO(O{\cdot}CH_2Ph)_2$, R′ = H], the hydrochloride of which was hydrogenolysed to give the crystalline 5-hydroxymethyl-2 : 4-dimethyl-3-pyridyl dihydrogen phosphate [I; R = $PO(OH)_2$, R′ = H]. This compound gave no

colour with ferric chloride and no reaction with Gibbs reagent, 2 : 6-dichloroquinone chloroimide, indicating that the phenol group was no longer free.

Phosphorolysis of aneurin acetate with anhydrous phosphoric acid had been used to prepare aneurin monophosphate (Morrison, Atherton, and Avison, B.P. 687,674).



(I)

Phosphorolysis of 5-acetoxymethyl-3-hydroxy-2 : 4-dimethylpyridine [I; R = H, R′ = AcO] therefore offered a route to the required dihydrogen phosphate [I; R = H, R′ = $PO(OH)_2$]. The acetate [I; R = CH_2Ph, R′ = AcO] was made by benzylating 4-deoxypyridoxine with benzyldimethylphenylammonium chloride, and acetylating the 3-benzyloxypyridine to give the 5-acetoxymethyl-compound [I; R = CH_2Ph, R′ = AcO] from which the benzyl group was hydrogenolysed. It was found to be unnecessary to carry out the last step, however, because, when the 3-benzyloxy-pyridine was heated with anhydrous phosphoric acid the phosphate [I; R = H, R′ = $PO(OH)_2$] was obtained, and was isolated, by means of its water-soluble barium salt, as the crystalline free acid. Benzyl phenyl ether gave phenol and benzyl dihydrogen phosphate when heated with anhydrous phosphoric acid under these conditions.

The deoxypyridoxine 5-phosphate [I; R = H, R′ = $PO(OH)_2$] was a moderately water-soluble, crystalline compound, giving a strongly positive Gibbs test at a dilution of 1 : 100,000 and a crimson colour with ferric chloride solution. Both phosphates inhibited dissociated tyrosine decarboxylase (cf. Umbreit and Waddell, *loc. cit.*), the 3-phosphate being about half as active as the 5-phosphate (Hawkins, unpublished work; Gale, personal communication).

Ultra-violet absorption measurements on some of the compounds described in this paper have been carried out by Lunn and Morton (*Analyst*, 1952, **77**, 718).

Experimental

Dibenzyl 5-Hydroxymethyl-2 : 4-dimethyl-3-pyridyl Phosphate [I; R = $PO(O{\cdot}CH_2Ph)_2$, R′ = H].—To 3-hydroxy-5-hydroxymethyl-2 : 4-dimethylpyridine hydrochloride (3·77 g.) in *tert.*-butanol containing 10% v/v of dry benzene (50 ml.), was added potassium *tert.*-butoxide (0·04 mole) in the same solvent. Tetrabenzyl pyrophosphate (10·7 g.) was added to the stirred mixture at 0° and stirring continued for 4 hr. Potassium chloride and potassium dibenzyl phosphate were filtered off and the filtrate was evaporated to dryness under reduced pressure. The residue was partitioned between chloroform and water. The chloroform layer was washed with ice-cold N-sodium hydroxide and distilled water, dried (Na_2SO_4), and evaporated under reduced pressure to give the dibenzyl phosphate as an oil (6·2 g.). The oil was dissolved in ether, the solution treated with charcoal and filtered, and the ester converted into its *hydrochloride*, which had m. p. 114—116° (from ethanol–ether) (6·2 g., 72%) (Found: C, 57·7; H, 5·9; N, 3·25; P, 7·2. $C_{22}H_{24}O_5NP,HCl$ requires C, 58·6; H, 5·6; N, 3·1; P, 6·9%).

5-Hydroxymethyl-2 : 4-dimethyl-3-pyridyl Dihydrogen Phosphate [I; R = $PO(OH)_2$, R′ = H].—The hydrochloride (4·5 g.) of the dibenzyl ester in 50% aqueous ethanol (50 ml.) was hydrogenolysed, a palladium–carbon catalyst (0·4 g.) being used (0·021 mole of hydrogen was taken up rapidly). The catalyst was filtered off and washed with distilled water, and the filtrate was concentrated to 25 ml. Acetone (200 ml.) was added and the precipitated crude *dihydrogen phosphate* crystallised from water–acetone, giving needles, m. p. 205—207° (1·4 g., 56%) (Found: C, 40·0; H, 5·0; N, 6·3; P, 13·0%; *M*, by titration, 237. $C_8H_{12}O_5NP$ requires C, 41·0; H, 5·1; N, 6·0; P, 13·4%; *M*, 233).

3-Benzyloxy-5-hydroxymethyl-2 : 4-dimethylpyridine (I; R = CH_2Ph, R′ = H).—3-Hydroxy-5-hydroxymethyl-2 : 4-dimethylpyridine hydrochloride (18·95 g.) was suspended in dry methanol. Benzyldimethylphenylammonium chloride (23·35 g.) and sodium methoxide (10·8 g.) in dry methanol were added, sodium chloride was filtered off, and the methanol solution was added dropwise during 1 hr. to boiling dry xylene (200 ml.). The methanol and some xylene distilled off during the addition, after which heating was continued for a further 1½ hr. The solution was cooled to room temperature and chloroform (*ca.* 300 ml.) was added. The solvent was then washed successively with distilled water, N-sodium hydroxide solution, and distilled water. Drying (Na_2SO_4), evaporation, and distillation at 0·3 mm. left a pinkish-grey solid which was recrystallised from benzene–light petroleum (b. p. 40—60°), to give the *3-benzyloxy*-compound, m. p. 72—73° (14·1 g., 58%) (Found: N, 5·5. $C_{15}H_{17}O_2N$ requires

N, 5·7%). The *hydrochloride*, formed quantitatively, had m. p. 183—185° (Found: C, 63·8; H, 6·6; N, 5·2; Cl^-, 12·6. $C_{15}H_{17}O_3N,HCl$ requires C, 64·2; H, 6·4; N, 5·0; Cl^-, 12·7%).

5-Acetoxymethyl-3-benzyloxy-2 : 4-dimethylpyridine (I; R = CH_2Ph, R′ = OAc).—The 3-benzyloxy-compound (I; R = CH_2Ph, R′ = H) (12·2 g.) was treated with acetic anhydride (30 ml.) in pyridine (30 ml.) for 24 hr. at room temperature. Pyridine and acetic anhydride were evaporated under reduced pressure; the residue was dissolved in water, the solution made alkaline with aqueous sodium hydrogen carbonate, and the product extracted into chloroform. The chloroform solution was dried, the solvent evaporated, and the *acetate* distilled *in vacuo*; it had b. p. 160—163°/0·3 mm. (11·4 g., 80%) (Found: C, 71·7; H, 7·0; N, 5·3; Ac, 14·5. $C_{17}H_{19}O_3N$ requires C, 71·6; H, 6·7; N, 4·9; Ac, 15·1%). The *hydrochloride*, recrystallised from ethyl acetate containing 2% of ethanol, had m. p. 161—163° (Found: N, 4·7; Cl^-, 11·6; Ac, 12·7. $C_{17}H_{19}O_3N,HCl$ requires N, 4·4; Cl^-, 11·1; Ac, 13·4%).

5-Acetoxymethyl-3-hydroxy-2 : 4-dimethylpyridine Hydrochloride.—The 3-benzyloxy-hydrochloride (2·7 g.) was hydrogenolysed in ethyl acetate–ethanol, a palladium–carbon catalyst being used. The catalyst was filtered off and ether added; the precipitated *3-hydroxy-hydrochloride*, crystallised from cold ethanol–ether, had m. p. 180—181° (1·2 g., 62%) (Found: C, 51·2; H, 5·95; N, 6·6; Cl^-, 16·3; Ac, 17·4. $C_{10}H_{13}O_3N,HCl$ requires C, 51·8; H, 6·1; N, 6·1; Cl^-, 15·3; Ac, 18·5%).

5-Hydroxy-4 : 6-dimethyl-3-pyridylmethyl Dihydrogen Phosphate [I; R = H, R′ = $PO(OH)_2$].—5-Acetoxymethyl-3-benzyloxy-2 : 4-dimethylpyridine (10·0 g.) was mixed with anhydrous phosphoric acid (34 g.), prepared by distilling the calculated amount of water from commercial 85% phosphoric acid at 120°/0·1 mm. The mixture was stirred under boiling dry toluene (500 ml.), which was distilled off at 60 ml./hr. The acetic acid which distilled over with the toluene was estimated by titration. After 4½ hr., 82% of the acetyl content of the starting material had been evolved as acetic acid. Heating was continued for a further 1½ hr. The mixture was cooled and the toluene decanted from the oily phosphoric acid layer which was dissolved in ice-cold water (100 ml.) and made alkaline (phenolphthalein) with saturated baryta solution. The barium phosphate precipitate was filtered off and thoroughly washed with distilled water (10 × 100 ml.). The combined aqueous filtrates were concentrated to 200 ml. under reduced pressure, filtered, and brought to pH 4·2 with sulphuric acid. Barium sulphate was removed on the centrifuge, and the supernatant liquor, and washings, concentrated to 100 ml., treated with charcoal (0·5 g.), and filtered. Acetone (600 ml.) was added to the filtrate and the crude dihydrogen phosphate filtered off after 24 hr. at 0°; recrystallisation from a mixture of water (50 ml.) and acetone (200 ml.) at 40° gave the crystalline dihydrogen phosphate, m. p. 251—252° (3·5 g., 43%) (Found: C, 40·3; H, 5·2; N, 6·1; P, 13·6%; *M*, by titration, 234. Calc. for $C_8H_{12}O_5NP$: C, 41·0; H, 5·1; N, 6·0; P, 13·4%; *M*, 233).

Cleavage of Benzyl Phenyl Ether with Anhydrous Phosphoric Acid.—Benzyl phenyl ether (3·5 g.) was heated at 110° with anhydrous phosphoric acid (35 g.) for 4 hr. The mixture was dissolved in ice–water, and the insoluble portion (1·9 g.) filtered off and recrystallised from ethanol [giving unchanged material (1·4 g.)]. From one portion of the acidic aqueous filtrate tribromophenol, m. p. 95° (1·1 g.), was prepared by the addition of bromine water. The second portion was made just alkaline (phenolphthalein) with barium hydroxide solution, and the barium salt of benzyl dihydrogen phosphate isolated (0·6 g.) after removal of barium phosphate on the centrifuge (Found: P, 9·8. Calc. for $C_7H_7O_4PBa$: P, 9·6%).

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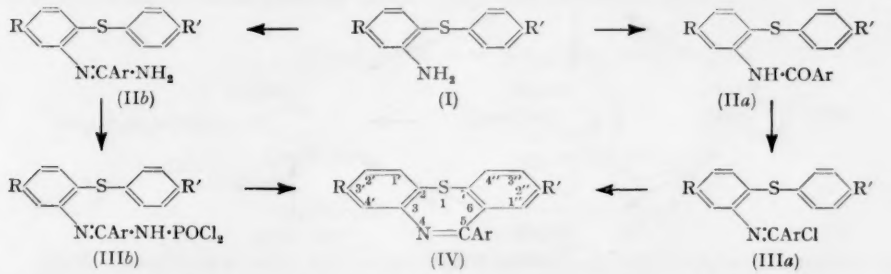
Heterocyclic Derivatives of 1 : 2-5 : 6-*Dibenzocyclohepta*-1 : 3 : 5-*triene. Part II.** 5-*Aryl*-2 : 3-6 : 7-*dibenzo*-1-*thia*-4-*aza*cyclo*hepta*-2 : 4 : 6-*trienes and their* 1 : 1-*Dioxides.**

By C. I. Brodrick, J. S. Nicholson, and W. F. Short.

[Reprint Order No. 5492.]

The thia-aza-compounds (IV) mentioned in the title are obtained from 2-benzamidodiphenyl sulphides (II*a*) or from the corresponding amidines (II*b*) and phosphoryl chloride. The seven-membered ring in these compounds is readily opened by methylating agents, giving a substituted benzophenone (VI). The 2'' : 3'-dibromo- and -dicyano-thia-aza-compounds are partly desulphurised when they are heated with cuprous bromide, being converted into 2 : 7-disubstituted phenanthridines. Oxidation of the thia-aza-compounds affords the corresponding 1 : 1-dioxides, which cannot be obtained from a 2-benzamidodiphenyl sulphone (VIII) or the related amidine (X), both of which yield an *NN'*-disubstituted amidine (XI) with phosphoryl chloride.

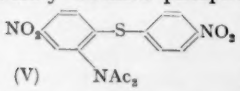
In Part I of this series * the preparation and properties of a number of 2 : 3-6 : 7-dibenz-1-oxa-4-aza*cyclo*hepta-2 : 4 : 6-trienes were described, and the present paper is concerned with compounds containing ·S· or ·SO_2· in place of the oxygen atom of the oxa-compounds. The thia-compounds (IV; R, R', Ar = H, H, Ph; H, NO_2, *p*-NO_2·C_6H_4; NO_2, NO_2, Ph; NO_2, NO_2, *p*-NO_2·C_6H_4; Br, Br, Ph, respectively) were prepared by dehydrating the corresponding 2-benzamidodiphenyl sulphides (II*a*) with phosphoryl chloride. The action of phosphoryl chloride on two of the amides under milder conditions afforded imidoyl chlorides (III*a*; R = R' = NO_2; Ar = Ph or *p*-NO_2·C_6H_4) and these chlorides, which were also obtained from the amides and phosphorus pentachloride, gave the thia-compounds (IV) on further treatment with phosphoryl chloride. Both imidoyl chlorides afforded 2-diacetylamino-4 : 4'-dinitrodiphenyl sulphide (V) on being boiled with acetic anhydride, whereas boiling formic acid reconverted them into the parent benzamido-compound (II*a*). *p*-Nitro-*N*-(5-nitro-2-*p*-nitrophenylthiophenyl)benzimidoyl chloride was hydrolysed by aqueous-alcoholic hydrochloric acid to 2-amino-4 : 4'-dinitrodiphenyl sulphide. 2-Amino-4-nitrodiphenyl sulphide, the intermediate required for the synthesis of 3'-nitro-5-phenyl-2 : 3-6 : 7-dibenzo-1-thia-4-aza*cyclo*hepta-2 : 4 : 6-triene, could not be obtained from 2 : 4-



dinitrodiphenyl sulphide: reduction of the dinitro-compound with sodium sulphide–sodium hydrogen carbonate gave diphenyl disulphide, also obtained from 2 : 4 : 4'-trinitrodiphenyl sulphide and sodium disulphide. Hodgson and Ward (*J.*, 1949, 136) and Ward and Day (*J.*, 1952, 398) have shown that *o*- and *p*-dinitrobenzenes are converted by sodium hydrogen sulphide into dinitrodiphenyl disulphide, but the total elimination of nitro-groups

* For nomenclature see Part I, Brodrick, Donaldson, Nicholson, Short, and Wibberley, *J.*, 1953, 1079.

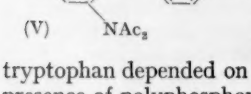
by alkaline sulphides, so far as we are aware, has not been recorded hitherto. The action of phosphoryl chloride on 2 : 4-dibenzamidodiphenyl sulphide and on 2 : 4-di-*p*-nitrobenzamidodiphenyl sulphide produced amorphous products, and 3′-benzamido-5-phenyl-2 : 3-6 : 7-dibenzo-1-thia-4-aza*cyclo*hepta-2 : 4 : 6-triene (IV; R = NHBz, R′ = H, Ar = Ph) and its dinitro-derivative could not be detected. Application of the synthesis to 2-benzamido-5′-chloro-2′-methyldiphenyl sulphide gave 1″-chloro-4″-methyl-5-phenyl-2 : 3-6 : 7-dibenzo-1-thia-4-aza*cyclo*hepta-2 : 4 : 6-triene (89%). It was noticed that if freshly distilled phosphoryl chloride was used in this cyclodehydration much starting material was recovered, a good yield being obtained only with the aged reagent, and this may also be applicable to the other examples. Snyder and Werber (*J. Amer. Chem. Soc.*, 1950, **72**, 2962) found that the yield of norharman from *N*-formyl-DL-tryptophan depended on the quality of the phosphoryl chloride used and showed that the presence of polyphosphoric acid leads to increased yields.



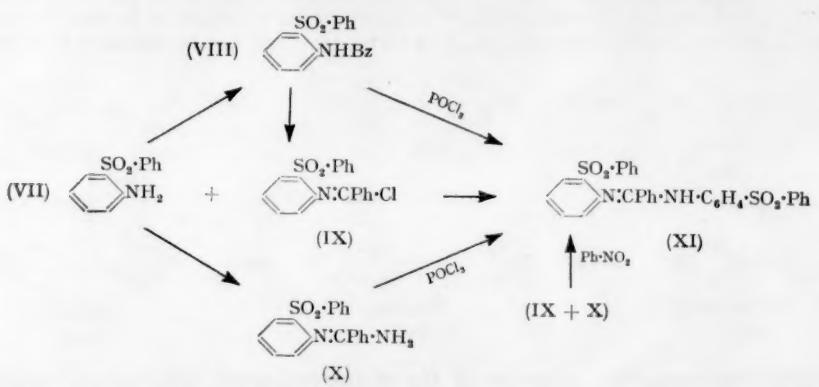
(V)

An alternative method for the preparation of the cyclic compounds is exemplified by the preparation of 5-phenyl-, 5-*p*-nitrophenyl-, and 5-*p*-methylsulphonylphenyl-2 : 3-6 : 7-dibenzo-1-thia-4-aza*cyclo*hepta-2 : 4 : 6-triene (IV; R = R′ = H; Ar = Ph, *p*-$NO_2{\cdot}C_6H_4$, *p*-$Me{\cdot}SO_2{\cdot}C_6H_4$) and of 2″-nitro-5-*p*-nitrophenyl-2 : 3-6 : 7-dibenzo-1-thia-4-aza*cyclo*hepta-2 : 4 : 6-triene (IV; R = H, R′ = NO_2, Ar = *p*-$NO_2{\cdot}C_6H_4$) from phosphoryl chloride and the corresponding *N*-(2-arylthioaryl)benzamidine (II*b*; R = H, H, H, H; R′ = H, H, H, NO_2; Ar = Ph, *p*-$NO_2{\cdot}C_6H_4$, *p*-$Me{\cdot}SO_2{\cdot}C_6H_4$, *p*-$NO_2{\cdot}C_6H_4$). In a subsequent communication it will be shown that certain amidines react with phosphoryl chloride to give aminophosphonyl dichlorides and it is probable that a compound of type (III*b*) is an intermediate in this synthesis.

The thia-aza-compounds, like the oxa-aza-analogues (Part I, *loc. cit.*), undergo fission of the heterocyclic nucleus when they are treated with methylating agents. Dr. A. E. S. Fairfull finds that 2″-nitro-5-*p*-nitrophenyl-2 : 3-6 : 7-dibenzo-1-thia-4-aza*cyclo*hepta-2 : 4 : 6-triene and methyl sulphate react at 200° to give a grey solid, probably the metho(methyl sulphate), converted into orange needles, m. p. 154—155°, by several crystallisations from methanol, the change being accelerated by the addition of a little water. This transformation product, which behaves as an amino-ketone, gives readily hydrolysed salts with mineral acids, is converted by methyl iodide and potassium carbonate



(VI)

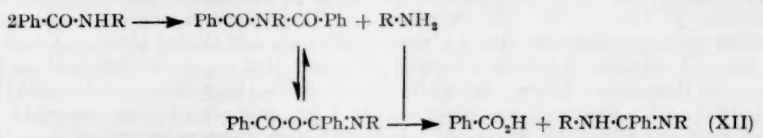


into a dimethyl compound, and is formulated as 2-*o*-methylaminophenylthio-4′ : 5-dinitrobenzophenone (VI).

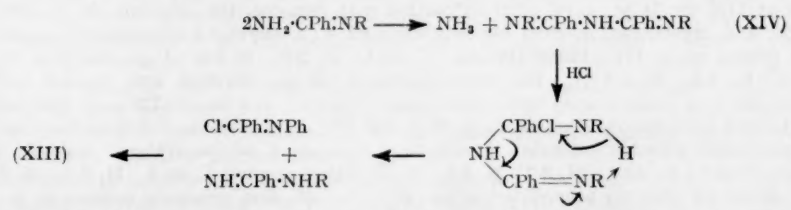
Another example of the fission of the heterocyclic nucleus was encountered during the conversion of 2″ : 3′-dibromo-5-phenyl-2 : 3-6 : 7-dibenzo-1-thia-4-aza*cyclo*hepta-2 : 4 : 6-triene into the corresponding dicyanide by the action of cuprous cyanide in boiling quinoline. In addition to 2″ : 3′-dicyano-5-phenyl-2 : 3-6 : 7-dibenzo-1-thia-4-aza*cyclo*hepta-2 : 4 : 6-

triene (47%), the product contained 2 : 7-dicyano-9-phenylphenanthridine (10%), identified by comparison with a specimen prepared from 2 : 7-diamino-9-phenylphenanthridine. The dicyano-thia-compound was not converted into the phenanthridine by cuprous cyanide in boiling quinoline, but cuprous bromide gave a very small yield of the dicyanophenanthridine. The dibromo-thia-compound was converted into 2 : 7-dibromo-9-phenylphenanthridine (20%) on being boiled with cuprous bromide–quinoline, and these reactions recall the production of carbazole by the heating of phenothiazine with copper powder (Goske, *Ber.*, 1887, **20**, 232). 9-Phenylphenanthridine could not be detected in the products of the action of cuprous bromide on 5-phenyl-2 : 3-6 : 7-dibenzo-1-thia-4-aza*cyclo*hepta-2 : 4 : 6-triene, and the *p*-substituents therefore seem to be necessary for the production of a diradical which is assumed to be an intermediate in the production of the phenanthridine.

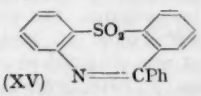
Attempts to adapt the two methods for the synthesis of the thia-compounds to the production of the corresponding thia-dioxides were unsuccessful. Both 2-benzamidodiphenyl sulphone (VIII) and *N*-(2-phenylsulphonylphenyl)benzamidine (X) were converted by phosphoryl chloride into an *NN'*-disubstituted amidine which must be *NN'*-di-(2-phenylsulphonylphenyl)benzamidine (XI), since it is also obtained from 2-aminodiphenylsulphone (VII) and *N*-(2-phenylsulphonylphenyl)benzimidoyl chloride (IX). The production of the amidine (XI) from the benzamido-compound (VIII) and phosphoryl chloride probably takes place as follows (cf. Oxley and Short, *J.*, 1946, 765) (R = *o*-Ph·SO_2·C_6H_4) :



Conversion of the amidine (X) into the substituted amidine (XI) probably involves the formation of the diamidide NR·CPh·NR·CPh:NH (XIII) which would be expected to decompose into the amidine (XII) and benzonitrile (Cooper, Partridge, and Short, *J.*, 1951, 396), and this amidine, and not the diamidide (XIII), was in fact obtained from the imidoyl chloride (IX) and the amidine (X). It has been shown (unpublished experiments with Mr. D. A. Firth) that certain amidines lose the elements of ammonia when they are treated with phosphoryl chloride and yield diamidides, but the results suggest that the amidine (X) would yield the diamidide (XIV). However, the diamidide (XIV) might be converted into its isomer (XIII) by addition of the elements of hydrogen chloride, followed by fission into an imidoyl chloride and an amidine, which then react to give (XIII), a series of reactions already exemplified by Cooper, Partridge, and Short (*loc. cit.*).



Cyclic thia-dioxides could not be obtained from *p*-nitro-*N*-(2-phenylsulphonylphenyl)-benzamidine and the corresponding *p*-methylsulphonylbenzamidine, and the failure of both methods is doubtless associated with the deactivation of the *ortho*-positions by the sulphonyl group.



(XV)

Oxidation of the thia-compounds (IV; R = H, H, NO_2; R' = H, NO_2, NO_2; Ar = Ph, *p*-NO_2·C_6H_4, Ph respectively) with hydrogen peroxide or chromic anhydride gave 5-phenyl-2 : 3-6 : 7-dibenzo-1-thia-4-aza*cyclo*hepta-2 : 4 : 6-triene-1 : 1-dioxide (XV) and its dinitro-derivatives.

Experimental

Preparation of Intermediates.

2-Benzamidodiphenyl Sulphide.—2-Aminodiphenyl sulphide hydrochloride (25 g.), m. p. 206—208°, prepared in 87% yield by the method of Roberts and Turner (*J.*, 1926, 1208), was added to a stirred mixture of benzene (75 c.c.) and water (170 c.c.), containing sodium hydroxide (4·2 g.), and the liberated amine was benzoylated by the simultaneous addition of aqueous sodium hydroxide (1·5 mols.) and benzoyl chloride (1 mol.) at 0—5°. The crude product (29 g.), isolated by extraction with benzene, crystallised from benzene–light petroleum and then from ethanol, giving *2-benzamidodiphenyl sulphide* as colourless needles, m. p. 66—67·5° (54%) (Found: N, 4·7. $C_{19}H_{15}ONS$ requires N, 4·6%).

4′-Nitro-2-p-nitrobenzamidodiphenyl Sulphide.—2-Amino-4′-nitrodiphenyl sulphide (20 g.), prepared as described by the Soc. Anon. des Mat. Col. et Prod. Chim. de St. Denis (B.P. 376,961), and *p*-nitrobenzoyl chloride (14·9 g.) were heated at 170° for 7 hr., and then at 225° until evolution of hydrogen chloride ceased. The crude product (29 g.), obtained by successive triturations with hot dilute alkali, dilute acid, and water, crystallised from 2-ethoxyethanol, giving *4′-nitro-2-p-nitrobenzamidodiphenyl sulphide* as yellowish-brown plates, m. p. 214—215° (Found: N, 10·8. $C_{19}H_{13}O_5N_3S$ requires N, 10·6%).

2-Benzamido-4 : 4′-dinitrodiphenyl Sulphide.—Nitration of *o*-chloroaniline in excess of sulphuric acid (de Bruyn, *Rec. Trav. chim.*, 1916, **36**, 126) gave 2-chloro-5-nitroaniline, m. p. 117—118° (86%), and this is the best method for the preparation of this amine (cf. Buchanan and Graham, *J.*, 1949, 3435). The chloro-amine (143 g.), sodium sulphide nonahydrate (292 g.), sodium hydrogen carbonate (102 g.), water (1650 c.c.), and alcohol (2400 c.c.) were refluxed for 90 min. A mixture of sodium hydrogen carbonate (102 g.), water (820 c.c.), and alcohol (820 c.c.) was then added, followed, after refluxing for 5 min., by *p*-chloronitrobenzene (140 g.) in alcohol (1650 c.c.). Refluxing was continued for 3 hr., and, after cooling overnight, the precipitated solid was filtered off, triturated successively with warm water and alcohol, dried, and extracted with hot ethyl acetate. Concentration of the extract gave 2-amino-4 : 4′-dinitrodiphenyl sulphide as an orange-brown solid (77 g.; m. p. 171—172·5°), which on recrystallisation from ethyl acetate formed orange-yellow, prismatic needles, m. p. 174—175·5° (Found: C, 49·3; H, 3·15; N, 14·05. $C_{12}H_9O_4N_3S$ requires C, 49·5; H, 3·1; N, 14·4%). *2-Benzamido-4 : 4′-dinitrodiphenyl sulphide*, obtained from the amine and benzoyl chloride in pyridine below 10°, crystallised from 2-ethoxyethanol in pale yellow needles, m. p. 200·5—201·5° (Found: N, 10·35. $C_{19}H_{13}O_5N_3S$ requires N, 10·6%).

4 : 4′-Dinitro-2-p-nitrobenzamidodiphenyl sulphide (63%), prepared similarly, separated from 2-ethoxyethanol in small pale yellow needles, m. p. 210—211° (Found: N, 12·35. $C_{19}H_{12}O_7N_4S$ requires N, 12·7%). When heated just below its m. p. this compound changes into a polymorphic form, m. p. 224—224·5°, so that the m. p. observed depends upon the rate of heating.

2-Benzamido-4 : 4′-dibromodiphenyl Sulphide.—4-Bromobenzenethiol (75·6 g.), 2 : 5-dibromonitrobenzene (112·4 g.), potassium hydroxide (25·6 g.), copper bronze (8 g.), and water (100 c.c.), heated at 175° for 7½ hr. gave, after extraction with benzene, the sulphide, m. p. 171—173° (67·5%), and crystallisation from benzene afforded *4 : 4′-dibromo-2-nitrodiphenyl sulphide* as yellow prisms, m. p. 172—173·5° (Found: C, 37·1; H, 2·0; N, 3·8. $C_{12}H_7O_2NBr_2S$ requires C, 37·0; H, 1·8; N, 3·6%). The nitro-compound (36 g.), reduced iron powder (120 g.), alcohol (510 c.c.), concentrated hydrochloric acid (1·5 c.c.), and water (720 c.c.) were refluxed for 22 hr. and gave the crude amine, m. p. 79·5—82° (90%). Crystallisation from ethyl acetate–light petroleum afforded colourless prisms of *2-amino-4 : 4′-dibromodiphenyl sulphide*, m. p. 80—82° (Found: C, 40·4; H, 2·7; N, 4·2. $C_{12}H_9NBr_2S$ requires C, 40·1; H, 2·5; N, 3·9%). Benzoylation afforded the *benzoyl* derivative (86%) in colourless, prismatic needles, m. p. 119—120·5° (Found: C, 49·1; H, 2·8; N, 3·4. $C_{19}H_{13}ONBr_2S$ requires C, 49·2; H, 2·8; N, 3·0%).

2 : 4-Dibenzamidodiphenyl Sulphide.—2 : 4-Dinitrodiphenyl sulphide was obtained in 66% yield by a modification of the method of Bogert and Evans (*Ind. Eng. Chem.*, 1926, **18**, 301) in which the reactants were heated at 150° for 6 hr. Attempts to reduce the 2-nitro-group by Raney nickel and hydrogen or stannous chloride in hydrochloric acid or acetic acid were unsuccessful. With sodium sulphide and sodium hydrogen carbonate in methanol, the only substance isolated was diphenyl disulphide, m. p. and mixed m. p. 59—60° (Found: C, 65·55; H, 4·6. Calc. for $C_{12}H_{10}S_2$: C, 66·0; H, 4·6%). The same compound was obtained in the attempted partial reduction of 2 : 4 : 4′-trinitrodiphenyl sulphide (Hodgson, *J.*, 1948, 2022) with sodium disulphide in aqueous alcohol. A mixture of the dinitro-compound (22 g.) and reduced

iron powder (32 g.), added to alcohol (300 c.c.), concentrated hydrochloric acid (5 c.c.), and water (480 c.c.) and refluxed with stirring for 3 hr., gave the crude base, m. p. 101—104° (13 g.). Crystallisation from aqueous alcohol gave 2 : 4-diaminodiphenyl sulphide, as buff needles, m. p. 106—108° (Found: N, 13·2. Calc. for $C_{12}H_{12}N_2S$: N, 13·0%). Bogert and Evans (*loc. cit.*) record m. p. 107°. The NN'-*dibenzoyl* derivative separated from methanol–acetone in solvated crystals, m. p. 120°, which after being dried at 80°/1 mm. had m. p. 169—169·5° (Found: N, 6·75. $C_{26}H_{20}O_2N_2S$ requires N, 6·6%). The *di*-p-*nitrobenzoyl* derivative crystallised from 2-ethoxyethanol in yellow, prismatic needles, m. p. 206—206·5° (Found: N, 10·7. $C_{26}H_{18}O_6N_4S$ requires N, 10·9%).

2-*Benzamido*-5'-*chloro*-2'-*methyldiphenyl Sulphide*.—5-Chloro-2-methylbenzenethiol (6·32 g.) (Sharp, *J.*, 1951, 2961; Archer and Suter, *J. Amer. Chem. Soc.*, 1952, **74**, 4296) and *o*-chloronitrobenzene (6·28 g.) were added, in that order, to a solution of sodium (1·3 g.) in alcohol (100 c.c.). The mixture was refluxed for 4 hr., cooled, and poured into water, and the precipitated solid was extracted with ether. Evaporation of the washed and dried extract to a small volume gave 5'-*chloro*-2'-*methyl*-2-*nitrodiphenyl sulphide* as bright yellow prisms, m. p. 79·5—81° (61%) (Found: C, 55·9; H, 3·5; N, 4·7. $C_{13}H_{10}O_2NClS$ requires C, 55·8; H, 3·6; N, 5·0%). The nitro-compound (31 g.) reduced iron powder (110 g.), alcohol (600 c.c.), water (900 c.c.), and concentrated hydrochloric acid (0·5 c.c.) were stirred and refluxed for 19 hr. Extraction with chloroform gave the *amine* as an oil (28 g.) which readily solidified, crystallisation from light petroleum (b. p. 40—60°) giving buff prisms, m. p. 59·5—61° (Found: N, 5·7. $C_{13}H_{12}NClS$ requires N, 5·6%). The *benzoyl* derivative (yield, 92%; m. p. 70—72·5°) crystallised from alcohol in colourless, feathery needles, m. p. 74—75·5° (Found: N, 4·3. $C_{20}H_{16}ONClS$ requires N, 4·0%).

2-*Benzamidodiphenyl Sulphone*.—2-Aminodiphenyl sulphone (1 g.; Ullmann, *Ber.*, 1901, **34**, 1153), pyridine (8 c.c.), and benzoyl chloride (0·7 g.) were kept at room temperature for 3 hr. and heated under reflux for ½ hr. The mixture was poured into dilute sulphuric acid, and the solid which separated was recrystallised from a little methanol giving the crude benzoyl derivative, m. p. 107—109° (75%). Recrystallisation from methanol gave 2-*benzamidodiphenyl sulphone* as colourless prisms, m. p. 111—112·5° (Found: N, 4·6. $C_{19}H_{15}O_3NS$ requires N, 4·15%).

N-(2-*Phenylthiophenyl*)*benzamidine*.—A mixture of 2-*aminodiphenyl sulphide benzenesulphonate* (5·38 g.), m. p. 225—226° (Found: N, 4·0. $C_{18}H_{17}O_3NS_2$ requires N, 3·9%), and phenyl cyanide (1·55 g.) was heated at 200° for 2 hr. The cooled melt was extracted with a large volume of hot water and the crude *amidine* (62%) was isolated by basification and extraction with chloroform. It crystallised from benzene–light petroleum in colourless plates, m. p. 103—104·5° (Found: N, 9·5. $C_{19}H_{16}N_2S$ requires N, 9·2%).

p-*Nitro*-N-(2-*phenylthiophenyl*)*benzamidine*, prepared similarly (47% yield), crystallised from benzene–light petroleum in fine yellow needles which were dried at 55°/1 mm. for 6 hr. and then had m. p. 108—109·5° (Found: N, 12·0. $C_{19}H_{15}O_2N_3S$ requires N, 12·0%). p-*Methylsulphonyl*-N-(2-*phenylthiophenyl*)*benzamidine* (yield, 70%) crystallised from chloroform–light petroleum in pale yellow cubes, m. p. 183—184° (Found: N, 7·3. $C_{20}H_{18}O_2N_2S_2$ requires N, 7·3%).

p-*Nitro*-N-(2-p-*nitrophenylthiophenyl*)*benzamidine*.—2-*Amino*-4'-*nitrodiphenyl sulphide benzenesulphonate*, prepared from its constituents, had m. p. 250—251° (Found: N, 7·2. $C_{18}H_{16}O_5N_2S_2$ requires N, 6·9%). This salt (8·1 g.) and *p*-nitrophenyl cyanide (3·35 g.) were heated at 200° for 2 hr. and the crude amidine was liberated by alkali, collected in ether, and recrystallised from benzene (2·26 g.; m. p. 140—143°). A second recrystallisation gave p-*nitro*-N-(2-p-*nitrophenylthiophenyl*)*benzamidine* as yellow prismatic needles, m. p. 156—157° (Found: N, 14·0. $C_{19}H_{14}O_4N_4S$ requires N, 14·2%).

N-(2-*Phenylsulphonylphenyl*)*benzamidine*.—2-Aminodiphenyl sulphone (5 g.) was converted into its benzenesulphonate (7·5 g.; m. p. 170°) with excess of benzenesulphonic acid in absolute alcohol. This salt (7·2 g.) and phenyl cyanide (1·8 g.) were heated at 210° for 4 hr., and the resulting glass was dissolved in warm alcohol and diluted with excess of 0·5N-hydrochloric acid before extraction of unchanged 2-aminodiphenyl sulphone with ether. The aqueous solution was basified with 2N-sodium hydroxide, and the crude amidine (3·55 g., m. p. 165°) was washed with water and crystallised from methanol, giving N-(2-*phenylsulphonylphenyl*)*benzamidine* as colourless prisms, m. p. 165—166·5° (Found: C, 67·6; H, 4·8; N, 8·5. $C_{19}H_{16}O_2N_2S$ requires C, 67·85; H, 4·8; N, 8·3%).

p-*Nitro*-N-(2-*phenylsulphonylphenyl*)*benzamidine*, prepared similarly in 33% yield, crystallised from 2-ethoxyethanol in pale yellow prisms, m. p. 254° (decomp.) (Found: N, 11·0. $C_{19}H_{15}O_4N_3S$ requires N, 11·0%).

p-*Methylsulphonyl*-N-(2-*phenylsulphonylphenyl*)*benzamidine* (53·5%) crystallised from 2-ethoxyethanol in colourless prisms, m. p. 248—250° (Found: N, 7·2. $C_{20}H_{18}O_4N_2S_2$ requires N, 6·8%).

5-Aryl-2 : 3-6 : 7-*dibenzo*-1-*thia*-4-*aza*cyclo*hepta*-2 : 4 : 6-*trienes from* 2-*Benzamidodiphenyl Sulphides.*

5-*Phenyl*-2 : 3-6 : 7-*dibenzo*-1-*thia*-4-*aza*cyclo*hepta*-2 : 4 : 6-*triene*.—2-Benzamidodiphenyl sulphide (18 g.), phosphoryl chloride (30 c.c.), and nitrobenzene (80 c.c.) were boiled under reflux for 4 hr. and then distilled under reduced pressure to remove the solvent. The residue was triturated with warm 5N-sodium hydroxide, and the crude thia-aza-compound was collected in benzene. Recrystallisation from methanol gave 5-*phenyl*-2 : 3-6 : 7-*dibenzo*-1-*thia*-4-*aza*cyclo*hepta*-2 : 4 : 6-*triene* (65%) as pale yellow needles, m. p. 117—118° (Found: C, 79·6; H, 4·4; N, 4·9; S, 11·0. $C_{19}H_{13}NS$ requires C, 79·4; H, 4·5; N, 4·9; S, 11·15%).

2″-*Nitro*-5-p-*nitrophenyl*-2 : 3-6 : 7-*dibenzo*-1-*thia*-4-*aza*cyclo*hepta*-2 : 4 : 6-*triene*.—(1) 4′-Nitro-2-*p*-nitrobenzamidodiphenyl sulphide (29 g.), phosphoryl chloride (68 c.c.), and nitrobenzene (200 c.c.), boiled for 5 hr. and worked up as in the preceding experiment, afforded a 69% yield of 2″-*nitro*-5-p-*nitrophenyl*-2 : 3-6 : 7-*dibenzo*-1-*thia*-4-*aza*cyclo*hepta*-2 : 4 : 6-*triene*, flocculent yellow needles, m. p. 229·5° (Found: C, 59·8; H, 2·9; N, 11·5. $C_{19}H_{11}O_4N_3S$ requires C, 60·5; H, 2·9; N, 11·1%).

(2) The amide (14·5 g.), phosphorus pentachloride (7·6 g.), and chlorobenzene (150 c.c.) were boiled under reflux for 2 hr., then treated with charcoal and filtered. The solvent was removed from the filtrate under reduced pressure, the residue was dissolved in ethyl acetate, and the solution concentrated and diluted whilst hot with light petroleum. The yellow prismatic needles which separated on cooling were recrystallised in the same way and gave p-*nitro*-N-(2-p-*nitrophenylthiophenyl*)*benzimidoyl chloride* (68%), m. p. 124—125° (Found: C, 55·2; H, 2·9; N, 10·4. $C_{19}H_{12}O_4N_3ClS$ requires C, 55·1; H, 2·9; N, 10·15%). When this imidoyl chloride was boiled with phosphoryl chloride and nitrobenzene it gave the thia-aza-compound, m. p. and mixed m. p. 229·5°.

2″ : 3′-*Dinitro*-5-*phenyl*-2 : 3-6 : 7-*dibenzo*-1-*thia*-4-*aza*cyclo*hepta*-2 : 4 : 6-*triene*.—(1) 2-Benzamido-4 : 4′-dinitrodiphenyl sulphide (17 g.), phosphoryl chloride (8·3 c.c., 2·1 mols.), and nitrobenzene (300 c.c.) were boiled under reflux for 4 hr. at 220° (oil-bath); the product, isolated as described in the previous examples, was recrystallised from ethyl acetate–chloroform, giving 2″ : 3′-*dinitro*-5-*phenyl*-2 : 3-6 : 7-*dibenzo*-1-*thia*-4-*aza*cyclo*hepta*-2 : 4 : 6-*triene* as pale yellow needles, m. p. 202—204° (63·5%) (Found: C, 61·05; H, 3·1; N, 11·2; S, 8·8. $C_{19}H_{11}O_4N_3S$ requires C, 60·5; H, 2·9; N, 11·1; S, 8·5%). When the amide (9·4 g.), phosphoryl chloride (36 c.c., 16·5 mols.), and nitrobenzene (145 c.c.) were refluxed at 200° for 4 hr. and worked up as in the cyclodehydration experiment, the concentrated chloroform solution gave a solid (7·46 g.), m. p. 125—130°, by addition of light petroleum. Two crystallisations from benzene gave N-(5-*nitro*-2-p-*nitrophenylthiophenyl*)*benzimidoyl chloride* as yellow needles, m. p. 130·5—132° (Found: C, 54·7; H, 3·15; N, 10·0. $C_{19}H_{12}O_4N_3ClS$ requires C, 55·1; H, 2·9; N, 10·15%). The imidoyl chloride (1·65 g.), m. p. and mixed m. p. 130·5—132°, was also obtained by boiling the amide (2 g.), phosphorus pentachloride (0·9 g.), and chlorobenzene (25 c.c.) for 2 hr. When the imidoyl chloride (0·5 g.) and formic acid (10 c.c.) were boiled for 1½ hr., a solid separated progressively and precipitation was completed by the addition of water (yield, 0·43 g.; m. p. 200·5—202°). Recrystallisation from ethyl acetate gave 2-benzamido-4 : 4′-dinitrodiphenyl sulphide, m. p. and mixed m. p. 201—202°. The imidoyl chloride (0·5 g.), fused sodium acetate (0·5 g.), and acetic anhydride (12 c.c.) were refluxed for 12 hr. and then evaporated to dryness under reduced pressure, and the residue was shaken with sodium hydrogen carbonate solution and extracted with chloroform. The residue from the washed and dried ($MgSO_4$) chloroform solution was recrystallised twice from ethyl acetate, giving colourless prisms of 2-diacetylamino-4 : 4′-dinitrodiphenyl sulphide, m. p. 165—166·5° (Found: N, 11·45. $C_{16}H_{13}O_6N_3S$ requires N, 11·2%). The same diacetyl-amine was obtained from *p*-nitro-*N*-(5-nitro-2-*p*-nitrophenylthiophenyl)benzimidoyl chloride (below), acetic anhydride, and sodium acetate (2) The imidoyl chloride (1 g.), phosphoryl chloride (0·5 c.c., 2·2 mols.), and nitrobenzene (18 c.c.) gave the thia-aza-compound, m. p. and mixed m. p. 199·5—201°, when boiled under reflux for 5 hr. at 220° (oil-bath).

2″ : 3′-*Dinitro*-5-p-*nitrophenyl*-2 : 3-6 : 7-*dibenzo*-1-*thia*-4-*aza*cyclo*hepta*-2 : 4 : 6-*triene*.—(1) 4 : 4′-Dinitro-2-*p*-nitrobenzamidodiphenyl sulphide (1 g.), phosphoryl chloride (0·5 c.c., 2·4 mols.), and nitrobenzene (18 c.c.) were refluxed for 4 hr. at 220°, cooled, and decomposed as in previous experiments, a large volume of chloroform being necessary for the extraction of the

product. Successive crystallisations from 2-ethoxyethanol and from ethyl acetate (by concentration of the dilute solution) gave bright yellow 2'' : 3'-*dinitro*-5-p-*nitrophenyl*-2 : 3-6 : 7-*dibenzo*-1-*thia*-4-*aza*cyclo*hepta*-2 : 4 : 6-*triene* (40%), m. p. 277—279° (Found : C, 54·4 ; H, 2·3 ; N, 13·5. $C_{19}H_{10}O_6N_4S$ requires C, 54·0 ; H, 2·4 ; N, 13·3%). When the amide (10 g.), phosphoryl chloride (35 c.c., 16·8 mols.), and nitrobenzene (180 c.c.) were refluxed at 200° for 5 hr., the crude product (7·84 g.), m. p. 197—199°, isolated as in previous cases, was purified by dissolution in boiling ethyl acetate (1 l.) (charcoal) and concentration to 150 c.c., giving bright yellow needles of p-*nitro*-N-(5-*nitro*-2-p-*nitrophenylthiophenyl*)*benzimidoyl chloride*, m. p. 205—205·5° (Found : C, 49·5 ; H, 2·7 ; N, 12·5. $C_{19}H_{11}O_6N_4ClS$ requires C, 49·7 ; H, 2·4 ; N, 12·2%). The same imidoyl chloride (1·25 g.) was obtained from the amide (2·2 g.), phosphorus pentachloride, and chlorobenzene under the conditions described for the dinitro-compound. When the imidoyl chloride was boiled with formic acid for 1 hr., 4 : 4'-dinitro-2-*p*-nitrobenzamidodiphenyl sulphide, m. p. and mixed m. p. 211—211·5°, was regenerated and was converted into the form of m. p. 224—224·5° by heating just below the m. p. 2-Amino-4 : 4'-dinitrodiphenyl sulphide, m. p. and mixed m. p. 175—176°, was obtained by boiling the imidoyl chloride (0·4 g.) with concentrated hydrochloric acid (10 c.c.) and alcohol (40 c.c.) for 17 hr. Boiling acetic anhydride and sodium acetate converted the imidoyl chloride into 2-diacetylamino-4 : 4'-dinitrodiphenyl sulphide, m. p. and mixed m. p. 163—166°.

(2) The imidoyl chloride (0·4 g.), phosphoryl chloride (0·25 c.c., 3·1 mols.), and nitrobenzene (10 c.c.) were boiled for 2 hr. and gave the thia-aza-compound, m. p. and mixed m. p. 274—276°.

2'' : 3'-*Dibromo*-5-*phenyl*-2 : 3-6 : 7-*dibenzo*-1-*thia*-4-*aza*cyclo*hepta*-2 : 4 : 6-*triene*.—2-Benzamido-4 : 4'-dibromodiphenyl sulphide (30 g.), phosphoryl chloride (60 c.c.), and nitrobenzene (360 c.c.) were refluxed for 2 hr. and worked up as in previous experiments. The residue from the evaporated chloroform extract was crystallised from benzene–light petroleum and gave the cyclic *compound*, the first crop (68%) having m. p. 154—155° and the second (10%) m. p. 152·5—154°. Recrystallisation of the first crop from the same solvent gave lemon-yellow prisms of unchanged m. p. (Found : C, 51·2 ; H, 2·7 ; N, 3·05 ; Br, 35·9. $C_{19}H_{11}NBr_2S$ requires C, 51·2 ; H, 2·5 ; N, 3·1 ; Br, 35·95%).

1''-*Chloro*-4''-*methyl*-5-*phenyl*-2 : 3-6 : 7-*dibenzo*-1-*thia*-4-*aza*cyclo*hepta*-2 : 4 : 6-*triene*, yellow hexagonal prisms from ethyl acetate, m. p. 165·5—166·5° (Found : C, 71·9 ; H, 4·15 ; N, 4·1. $C_{20}H_{14}NClS$ requires C, 71·5 ; H, 4·2 ; N, 4·2%), was obtained from 2-benzamido-5'-chloro-2'-methyldiphenyl sulphide (1·37 g.) and phosphoryl chloride (9 c.c.) in 3½ hr. The yield was 89% when an old sample of phosphoryl chloride was employed, but much starting material was recovered when freshly distilled phosphoryl chloride was used.

5-*Aryl*-2 : 3-6 : 7-*dibenzo*-1-*thia*-4-*aza*cyclo*hepta*-2 : 4 : 6-*trienes from* N-(2-*Arylthioaryl*)*benzamidines*.

A mixture of the amidine, nitrobenzene (15 c.c. per g.), and phosphoryl chloride (7—9 mols.) was boiled under reflux for 4—5 hr., liquids were removed by distillation under reduced pressure, and the residue was triturated with 5N-sodium hydroxide before being extracted with chloroform. The chloroform solution was concentrated, and the thia-aza-compound was precipitated by the addition of light petroleum and recrystallised from benzene–light petroleum.

5-Phenyl- and 2''-nitro-5-*p*-nitrophenyl-2 : 3-6 : 7-dibenzo-1-thia-4-aza*cyclo*hepta-2 : 4 : 6-trienes, prepared by this method in 70% and 44% yield respectively, were identical (mixed m. p.s) with specimens prepared from the amides (above). 5-p-*Nitrophenyl*-2 : 3-6 : 7-*dibenzo*-1-*thia*-4-*aza*cyclo*hepta*-2 : 4 : 6-*triene* (28%) crystallised in yellow prisms, m. p. 141—142° (Found: C, 69·5 ; H, 3·6 ; N, 8·5. $C_{19}H_{12}O_2N_2S$ requires C, 68·65 ; H, 3·6 ; N, 8·4%). 5-p-*Methylsulphonylphenyl*-2 : 3-6 : 7-*dibenzo*-1-*thia*-4-*aza*cyclo*hepta*-2 : 4 : 6-*triene* was obtained in 61% yield as yellow prismatic needles, m. p. 191—191·5° (Found : C, 65·6 ; H, 4·0 ; N, 4·2. $C_{20}H_{15}O_2NS_2$ requires C, 65·75 ; H, 4·1 ; N, 3·8%).

Miscellaneous Reactions.

2''-*Nitro*-5-p-*nitrophenyl*-2 : 3-6 : 7-*dibenzo*-1-*thia*-4-*aza*cyclo*hepta*-2 : 4 : 6-*triene and Methyl Sulphate* (Experiments by Dr. A. E. S. Fairfull).—The nitro-compound (3 g.) and methyl sulphate (4·5 c.c.) were boiled for 4 min., cooled, and diluted with ether. The gum which separated was washed with methanol, giving a grey solid (4·1 g.). A solution of this solid (0·4 g.) in methanol (100 c.c.) was evaporated to give orange needles (0·25 g.), m. p. 148—152°, and the change was hastened by adding a few drops of water to the methanol. Crystallisation from ethanol gave 2-o-*methylaminophenylthio*-4' : 5-*dinitrobenzophenone*, m. p. 154—155° (Found : C, 58·6 ; H, 3·8 ; N, 10·2. $C_{20}H_{15}O_5N_3S$ requires C, 58·7 ; H, 3·7 ; N, 10·3%), converted by

48% hydrobromic acid into an unstable *hydrobromide*, m. p. 185—187° (decomp.), which reverted to its progenitors with alcohol or water (Found: N, 8·2. $C_{20}H_{16}O_5N_3BrS$ requires N, 8·6%). The amino-ketone (0·6 g.), methyl iodide (10 c.c.), and potassium carbonate (1 g.) were stirred and boiled under reflux for 100 hr., and the filtered solution was then evaporated and the residue (0·41 g., m. p. 128—133°) crystallised successively from ethanol and benzene–light petroleum, giving 2-o-*dimethylaminophenylthio*-4′: 5-*dinitrobenzophenone* as red prisms, m. p. 141—142° (Found: C, 59·5; H, 4·3; N, 9·7, 9·9. $C_{21}H_{17}O_5N_3S$ requires C, 59·6; H, 4·0; N, 9·9%). On admixture with the monomethyl compound the m. p. was depressed to 122—124°.

2″-*Amino*-5-p-*aminophenyl*-2 : 3-6 : 7-*dibenzo*-1-*thia*-4-*aza*cyclo*hepta*-2 : 4 : 6-*triene* (With Dr. T. I. Watkins).—The dinitro-compound (11·4 g.), stannous chloride dihydrate (61·5 g.), concentrated hydrochloric acid (90 c.c.), and alcohol (150 c.c.) were stirred and heated under reflux for 1·5 hr. The alcohol was evaporated under reduced pressure and the cooled residual solution was poured slowly into 30% aqueous sodium hydroxide (300 c.c.) with stirring, the temperature being kept below 10°. The precipitated *diamine* was isolated and crystallised from a large volume of alcohol in pale yellow rhombs, m. p. 216—217° (57%) (Found: C, 72·0; H, 4·85; N, 13·45. $C_{19}H_{15}N_3S$ requires C, 71·9; H, 4·75; N, 13·25%). The *diacetyl* derivative separated from alcohol in small, yellow needles, m. p. 288—289° (Found: N, 10·7. $C_{23}H_{19}O_2N_3S$ requires N, 10·5%). The *diethoxycarbonyl* derivative, prepared in 74% yield by treating the diamine in alcohol with ethyl chloroformate (2 mols.) in presence of excess of diethylaniline, formed colourless plates (from alcohol), m. p. 187—188° (Found: N, 9·4. $C_{25}H_{23}O_4N_3S$ requires N, 9·1%). When an excess of ethyl chloroformate was used the product was the tetraethoxycarbonyl derivative, yellow needles, m. p. 234—236° (Found: N, 6·5. $C_{31}H_{31}O_8N_3S$ requires N, 6·8%).

2″ : 3′-*Dicyano*-5-*phenyl*-2 : 3-6 : 7-*dibenzo*-1-*thia*-4-*aza*cyclo*hepta*-2 : 4 : 6-*triene*.—The corresponding dibromo-compound (4·45 g.) and cuprous cyanide (3·6 g., 4 mols.) were ground together and added during 30 min. to boiling quinoline (30 c.c.). The mixture was refluxed for a further 30 min., cooled, and poured into 5N-hydrochloric acid (300 c.c.), and water (1 l.) was added. The precipitated solid was filtered off, washed with water, dried, and exhaustively extracted with hot chloroform. Evaporation of the combined extracts gave a residue which was treated with hot ethyl acetate (30 c.c.). The insoluble material (0·4 g.; m. p. 313—315°), which recrystallised from 2-ethoxyethanol as colourless needles, m. p. 317—318°, was identified as 2 : 7-dicyano-9-phenylphenanthridine by analysis (Found: C, 82·9; H, 3·8; N, 13·9. Calc. for $C_{21}H_{11}N_3$: C, 82·6; H, 3·6; N, 13·8%) and comparison with an authentic specimen, m. p. 314—316°, prepared by the method of Libman and Slack (*J.*, 1951, 2588) who record m. p. 302°. Concentration of the ethyl acetate filtrate (above) and addition of light petroleum gave the *dicyanide* (60%), m. p. 216—219°, which was obtained as fine, pale yellow needles, m. p. 224—225° (Found: C, 74·6; H, 2·9; N, 12·8. $C_{21}H_{11}N_3S$ requires C, 74·75; H, 3·25; N, 12·5%), after two crystallisations from ethyl acetate and one from benzene. The dicyanide was unchanged on further treatment with cuprous cyanide under the conditions used for its preparation, but with cuprous bromide, after 1·5 hr., 2 : 7-dicyano-9-phenylphenanthridine was formed in *ca.* 0·5% yield.

Action of Cuprous Bromide on 2″ : 3′-*Dibromo*-5-*phenyl*-2 : 3-6 : 7-*dibenzo*-1-*thia*-4-*aza*cyclo*hepta*-2 : 4 : 6-*triene*.—The dibromo-compound (4·4 g.), cuprous bromide (5·7 g.), and quinoline (40 c.c.) were refluxed for 3 hr. and the dark mixture was worked up as described in the similar experiment using cuprous cyanide. The chloroform-soluble extract was crystallised from ethyl acetate to give a mixture of yellow prisms (0·5 g.), m. p. 146—149°, raised to 156—157° by recrystallisation from ethyl acetate and identified as starting material by a mixed m. p. determination, and almost colourless needles (1·12 g.), m. p. 197·5—199°. The latter, after two crystallisations from ethyl acetate, had m. p. 200·5—201·5° (Found: C, 55·5; H, 2·7; N, 3·4; Br, 38·1. Calc. for $C_{19}H_{11}NBr_2$: C, 55·2; H, 2·7; N, 3·4; Br, 38·7%), undepressed on admixture with 2 : 7-dibromo-9-phenylphenanthridine, m. p. 200—201°, prepared according to Ritchie (*J. Proc. Roy. Soc. N.S.W.*, 1945, **78**, 141) who records m. p. 201°.

5-*Phenyl*-2″: 3′-*bis*-N-*phenylamidino*-2 : 3-6 : 7-*dibenzo*-1-*thia*-4-*aza*cyclo*hepta*-2 : 4 : 6-*triene*.—A powdered, intimate mixture of the dicyanide (5·8 g.) and anilinium benzenesulphonate (8·5 g.) was heated at 210° for 2¾ hr. with occasional stirring. After being cooled, the melt was dissolved in alcohol (charcoal) and basified with aqueous ammonia. The yellow precipitate was filtered off, washed with water, and dissolved in dilute acetic acid. This solution was boiled with charcoal for a few minutes, filtered, and again basified with ammonia. The precipitated diamidine, which could not be obtained crystalline, was purified by two treatments of its benzene solution with charcoal and reprecipitation with light petroleum, to give a yellow solid (4·6 g.), m. p. 144—148°, which was still partly hydrated after being dried at 100° [Found: C, 74·3; H, 4·6;

N, 12·95; H_2O (Karl Fischer), 1·15. $C_{33}H_{25}N_5S,0{\cdot}33H_2O$ requires C, 74·8; H, 4·85; N, 13·2; H_2O, 1·1%].

NN′-*Di*-(2-*phenylsulphonylphenyl*)*benzamidine*.—(1) *N*-(2-Phenylsulphonylphenyl)benzamidine (2·5 g.), phosphoryl chloride (15 c.c.), and nitrobenzene (35 c.c.) were boiled under reflux for 4 hr. and liquids were then removed at 100° under reduced pressure. The residue was dissolved in a small volume of warm methanol, the solution was diluted with 5N-hydrochloric acid, and the precipitated oil was collected in chloroform. Evaporation of the solvent afforded a solid (0·5 g.) which was recrystallised successively from methanol and ethyl acetate, giving NN′-*di*-(2-*phenylsulphonylphenyl*)*benzamidine* as large rods, m. p. 214—215° (Found: C, 67·25; 67·2; H, 4·6, 4·95; N, 5·4, 5·5. $C_{31}H_{24}O_4N_2S_2$ requires C, 67·4; H, 4·35; N, 5·1%).

(2) 2-Benzamidodiphenyl sulphone (2 g.), phosphorus pentachloride (1·4 g.), and dry benzene (10 c.c.) were refluxed for 30 min., then freed from liquids by distillation finally at 100°/1 mm., and the residue crystallised from benzene–light petroleum (b. p. 60—80°), giving crude *N*-(2-phenylsulphonylphenyl)benzimidoyl chloride (1·7 g.), m. p. 118—120°. Recrystallisation from the same solvent gave cream-coloured rods, m. p. 126—129°, but the crude material was used in subsequent experiments. The imidoyl chloride (1 g.), 2-aminodiphenyl sulphone (0·86 g.), and nitrobenzene (10 c.c.) were heated at 200° for 3 hr. and the crude amidine (1·37 g.), isolated as described in (1), was crystallised from acetic acid, giving the pure amidine (61%), m. p. 213—214°, undepressed on admixture with the sample prepared as above.

(3) The imidoyl chloride (1 g.), *N*-(2-phenylsulphonylphenyl)benzamidine (1·9 g.), and nitrobenzene (10 c.c.), heated at 200—210° for 3 hr., gave the crude amidine (1·5 g.), which on crystallisation from acetic acid gave the pure compound (46%), m. p. and mixed m. p. 212—214° (Found: C, 67·5; H, 4·4; N, 4·8%).

(4) 2-Benzamidodiphenyl sulphone (1 g.), phosphoryl chloride (2 c.c.), and nitrobenzene (10 c.c.) were refluxed for 4 hr., nitrobenzene was then removed under reduced pressure, and the residue crystallised from methanol. The first crystals to separate (0·3 g.) consisted of 2-aminodiphenyl sulphone, m. p. and mixed m. p. 119—120°, and *NN′*-di-(2-phenylsulphonylphenyl)-benzamidine (0·02 g.) was then deposited and had m. p. and mixed m. p. 213—214°.

5-*Phenyl*-2 : 3-6 : 7-*dibenzo*-1-*thia*-4-*aza*cyclo*hepta*-2 : 4 : 6-*triene* 1 : 1-*Dioxide*.—(1) Chromic anhydride (1·3 g.) was added to a solution of the thia-aza-compound (1 g.) in acetic acid (30 c.c.), the mixture was warmed cautiously, refluxed for 15 min., and poured into water. The yellow amorphous precipitate was crystallised from methanol, giving the crude *dioxide* (36%), m. p. 183—185°, raised by two further crystallisations to 188—189° (Found: C, 72·3, 72·1; H, 4·0, 4·15; N, 4·4. $C_{19}H_{13}O_2NS$ requires C, 71·5; H, 4·1; N, 4·4%). (2) 27% Hydrogen peroxide (1 c.c.) was added to a solution of the thia-aza-compound (0·2 g.) in acetic acid (8 c.c.); the mixture was kept at room temperature for 2 hr. and then at 50° for 2 hr. More hydrogen peroxide (0·5 c.c.) was then added, and, after the temperature had been kept at 75° for 1 hr. and at 90° for 1 hr., the mixture was poured into water. The solid was collected and recrystallised from methanol, giving the crude dioxide (45%), m. p. 186—188°, raised to 188—189° by a further crystallisation.

2″ : 3′-*Dinitro*-5-*phenyl*-2 : 3-6 : 7-*dibenzo*-1-*thia*-4-*aza*cyclo*hepta*-2 : 4 : 6-*triene* 1 : 1-*Dioxide*.—27% Hydrogen peroxide (32 c.c.) was added in 4 portions during 5 hr. to a solution of the thia-aza-compound (4 g.) in acetic acid (800 c.c.) at 90°. The mixture was kept at 90° for another 12 hr., cooled, filtered, and diluted with water. The solid was crystallised from acetic acid, giving the *dioxide* as yellow prisms (41·5%), m. p. 256—259°, raised to 259—259·5° by further crystallisation (Found: C, 55·9; H, 2·7; N, 10·3. $C_{19}H_{11}O_6N_3S$ requires C, 55·75; H, 2·7; N, 10·3%).

2″-*Nitro*-5-p-*nitrophenyl*-2 : 3-6 : 7-*dibenzo*-1-*thia*-4-*aza*cyclo*hepta*-2 : 4 : 6-*triene* 1 : 1-*dioxide*, obtained in 62% yield by the method used for the preparation of its isomer, crystallised from acetic acid in yellow prisms, m. p. 252—254° (Found: C, 55·3; H, 2·7; N, 10·65. $C_{19}H_{11}O_6N_3S$ requires C, 55·75; H, 2·7; N, 10·3%).

2″ : 3′-*Diamino*-5-*phenyl*-2 : 3-6 : 7-*dibenzo*-1-*thia*-4-*aza*cyclo*hepta*-2 : 4 : 6-*triene* 1 : 1-*Dioxide*.—(1) The corresponding nitro-compound (5·15 g.) was added during ½ hr. to a solution of stannous chloride dihydrate (51 g.) in absolute ethanol (65 c.c.), and the resulting red solution was refluxed for 1 hr., acidified with concentrated hydrochloric acid (50 c.c.), and distilled under reduced pressure to remove the alcohol. The residue was poured into excess of 5N-sodium hydroxide at 0°, the solid which separated was washed with water and dissolved in hot methanol, and the solution concentrated to a small volume, giving the crude product (63%), m. p. 283—284°. Recrystallisation from methanol gave the *diamine* as yellow prisms, m. p. 285—287° (Found: C, 64·8; H, 4·4; N, 11·6. $C_{19}H_{15}O_2N_3S$ requires C, 65·3; H, 4·3; N, 12·0%). (2) A solution

of the nitro-compound (1 g.) in ethyl acetate (200 c.c.) was shaken with Raney nickel (2 g.) and hydrogen under atmospheric conditions for 24 hr., and gave a somewhat lower yield of the diamine.

*2''-Amino-5-*p*-aminophenyl-2 : 3-6 : 7-dibenzo-1-thia-4-aza*cyclo*hepta-2 : 4 : 6-triene* 1 : 1-*dioxide*, prepared similarly, was obtained in 76% yield by stannous chloride reduction and in 37% yield by catalytic reduction of the dinitro-compound. The *diamine* separated from ethyl acetate in solvated form, m. p. 160° (decomp.), which lost solvent on crystallisation from methanol which gave yellow prisms, m. p. 213—215° (Found : C, 64·8; H, 4·8; N, 12·2. $C_{19}H_{15}O_2N_3S$ requires C, 65·3; H, 4·3; N, 12·0%).

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Two Serologically Active Polysaccharides from Bacillus anthracis.

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Two polysaccharides, designated I and II, have been isolated from *B. anthracis*. Polysaccharide I, which is precipitated by rabbit anti-anthrax sera, is a lightly phosphorylated mannan. Polysaccharide II, which is precipitated by horse anti-anthrax sera, is made up of D-galactose and *N*-acetyl-D-glucosamine in the molar ratio 2 : 1. The relation of these polysaccharides to those previously isolated from *B. anthracis* is discussed briefly.

IN addition to the capsular polypeptide (Iványovics and Brückner, *Z. Immunitäts.*, 1937, **90**, 304; 1938, **93**, 119; Hanby and Rydon, *Biochem. J.*, 1946, **40**, 297), *Bacillus anthracis* has long been known to elaborate other antigenic or haptenic substances one, at least, of which is a polysaccharide (Tomcsik, *Magyar Orv. Arch.*, 1927, **28**, 572; Schockaert, *Compt. rend. Soc. Biol.*, 1928, **99**, 1242; Combiesco, Soru and Stamatesco, *Arch. Roum. Path. exp. Microbiol.*, 1929, **2**, 291; Sordelli, Deulofeu and Ferrari, *Folia biol.*, 1932, **1**, 94; Tomcsik and Szongott, *Z. Immunitäts.*, 1932, **76**, 214). A well-defined polysaccharide was first isolated from *B. anthracis* by Iványovics (*Zentr. Bakt., Abt. I., Orig.*, 1939, **144**, 244; Rep. Proc. 3rd Intern. Congr. Microbiol., 1939, p. 785), who later showed it to be composed mainly of D-galactose and *N*-acetyl-D-glucosamine (Iványovics, *Z. Immunitäts.*, 1940, **97**, 402). There is, however, abundant and convincing serological evidence for the existence of a second polysaccharide (Zozaya, *J. Exp. Med.*, 1931, **54**, 725; Staub and Grabar, *Ann. Inst. Pasteur*, 1944, **70**, 16; Grabar and Staub, *ibid.*, p. 129) and our work had as its objective the isolation of both polysaccharides in a state of purity with a view to determining their structure.

The crude mixture of polysaccharides, obtained by ethanol precipitation of bacterial autolysates or, more conveniently, culture filtrates, was fractionated by precipitation with barium hydroxide (cf. Iványovics, *loc. cit.*), the fractionation being followed serologically. By a fortunate chance, we, unlike most previous workers, used a rabbit, rather than a horse, anti-anthrax serum for controlling our purification procedure and our isolation of two serologically active polysaccharides is probably due to this. Iványovics (*loc. cit.*) found the polysaccharide precipitated by barium hydroxide to be serologically inactive towards his horse anti-serum and accordingly discarded it as a non-specific impurity; we, on the other hand, found that, with our rabbit anti-serum, it was the baryta-precipitated polysaccharide, which we term " polysaccharide I," which was serologically active, the fraction not so precipitated (" polysaccharide II ") being inactive although clearly chemically similar to Iványovics's polysaccharide; Iványovics (*Z. Immunitäts.*, 1940, **98**, 373) had previously observed that rabbit anti-anthrax serum differed from the horse anti-serum in not agglutinating type XIV pneumococci.

Polysaccharide I had $[\alpha]_D^{19}$ +72·6° and gave a precipitate with the rabbit anti-serum at

dilutions down to 1 in 512 × 10^4; it gave only a slight precipitate, indicating the presence of less than 0·2% of polysaccharide II, with the horse anti-serum. Examined in the Tiselius electrophoresis apparatus in phosphate buffer of pH 8·0, it migrated very rapidly towards the anode as a broad single peak. The reducing power, determined by the method of Hagedorn and Jensen (*Biochem. Z.*, 1923, **135**, 46; **137**, 92), was 2·6%, corresponding to an average molecular weight of 6500 (38·5 hexose residues); the reducing value after hydrolysis reached a maximum value of 91% after 6 hours in 0·5N-hydrochloric acid at 100°.

Colour reactions indicated the presence of aldohexoses, and absence of hexoseamines; paper chromatograms of acid hydrolysates of polysaccharide I showed only a single spot, corresponding to mannose, and the presence of D-mannose was finally established by isolation of its *N*-methyl-*N*-phenylhydrazone. Colorimetric estimation, by Dische's carbazole–sulphuric acid reagent (*Mikrochem.*, 1930, **8**, 4; cf. Gurin and Hood, *J. Biol. Chem.*, 1939, **131**, 211; Siebert and Atno, *ibid.*, 1946, **163**, 511; Knight, *J. Exp. Med.*, 1947, **85**, 99), showed 98·5% of mannose after hydrolysis with 0·5N-sulphuric acid. at 100° for 6 hours.

On oxidation of polysaccharide I with periodic acid a maximum consumption of 1·14 moles of reagent per hexose residue was attained in 46 hours. Methylation (Haworth, *J.*, 1915, **107**, 8) and hydrolysis, followed by paper chromatography, showed the presence of a di-*O*-methyl- and a tri-*O*-methyl-mannose; the latter was identified as 2 : 3 : 6-tri-*O*-methyl-D-mannose by direct isolation and by conversion into the aniline derivative and comparison with an authentic specimen. These findings can be reconciled with various possible structures for polysaccharide I.

There is, however, no doubt that polysaccharide I is a D-mannan; of the various mannans which have been described it most closely resembles that recently isolated from yeast by Fischer, Kohtes, and Fellig (*Helv. Chim. Acta*, 1951, **34**, 1132). The small amount of phosphorus (0·9%) found in polysaccharide I would correspond to phosphorylation of one in twenty of the mannose residues; such phosphorylation would be in accord with the observed high electrophoretic mobility.

The relation of polysaccharide I to products obtained from *B. anthracis* by earlier workers is uncertain. Staub and Grabar (*loc. cit.*) obtained both Iványovics's polysaccharide and another, which they termed polysaccharide "*a*," by fractional precipitation of the glycoproteins of anthrax œdema fluid; our polysaccharide I is clearly not identical with "*a*," since it gives no precipitate with the horse anti-serum, but it may be a degraded form of "*a*."

Polysaccharide II had $[\alpha]_D^{20}$ +61·0° and gave only a trace of precipitate with the rabbit anti-serum at a dilution of 1 in 8 × 10^4, whereas it was highly active in precipitating the horse anti-serum; it caused no inhibition of the precipitation of polysaccharide I by the rabbit anti-serum. In the Tiselius electrophoresis apparatus, in phosphate buffer of pH 8·0, it formed a single sharp, slightly asymmetric peak which migrated very slowly towards the anode, showing no signs of inhomogeneity. The reducing power, determined by the method of Fairbridge, Willis, and Booth (*Biochem. J.*, 1951, **49**, 423), was 2·3%, corresponding to an average molecular weight of 7300. The liberation of reducing sugars on hydrolysis with 0·5N-hydrochloric acid at 100° was followed by several methods; the results indicate a 93% yield after 6 hours' hydrolysis.

Colour reactions indicated the presence of hexoseamine and aldohexose in polysaccharide II. Paper chromatograms of acid hydrolysates showed two spots, one corresponding to glucosamine and the other to galactose. D-Glucosamine was identified by isolation of the hydrochloride and the 2 : 4-dinitrophenyl derivative, and D-galactose by isolation of the *N*-methyl-*N*-phenylhydrazone. The liberation of glucosamine on acid hydrolysis was followed by the methods of Palmer, Smyth, and Meyer (*J. Biol. Chem.*, 1937, **119**, 491) and Tracey (*Biochem. J.*, 1952, **52**, 266); the mean maximum yield was 31·5%. A maximum yield of 62% of galactose was obtained on hydrolysis at 100° with 0·5N-sulphuric acid for 2 hours. The acetyl content of polysaccharide II was 7·0%.

These analytical data point very clearly to the conclusion that polysaccharide II contains D-galactose and *N*-acetyl-D-glucosamine residues in the molar ratio 2 : 1; on the assumption that our freeze-dried material contained 12% of water, all the analytical data, with the exception of the nitrogen content, are in satisfactory agreement with a molecule

containing 26 galactose and 13 *N*-acetylglucosamine residues. Periodic acid oxidation showed a maximal consumption of 0·74 mole of reagent per hexose unit in 40 hours; this is in agreement with oxidative splitting of the galactose residues, the acetylglucosamine residues remaining unaffected, but does not permit any very definite structural conclusion to be reached. Unfortunately, attempts to methylate the polysaccharide failed owing to extensive decomposition (cf. Stacey, *Adv. Carbohydrate Chem.*, 1946, **2**, 205).

Iványovics's preparation of the hexoseamine-containing polysaccharide of *B. anthracis* was found by him to contain galactose and acetylglucosamine in equimolecular proportion; the same ratio has very recently been reported in a polysaccharide isolated from *B. anthracis* grown *in vivo* (Smith and Zwartouw, *Biochem. J.*, 1954, **56**, viii). The difference between our 2 : 1 molar ratio and Iványovics's 1 : 1 ratio is striking in view of the fact that both preparations were made by similar methods and had almost identical optical rotations. It is possible that the repeated treatment with barium hydroxide which we employed to remove the last traces of polysaccharide I brings about preferential removal of glucosamine residues from a precursor with a non-uniform distribution of galactose and glucosamine residues; some such non-uniformity in our own material is suggested by our finding that the liberation of galactose on acid hydrolysis is much faster than that of glucosamine.

It is noteworthy that our polysaccharide II, like those prepared by Iványovics and by Smith and Zwartouw (*locc. cit.*), contains considerably more nitrogen than corresponds to the glucosamine content; in our case only 70%, in Iványovics's case only 60—65% and in Smith and Zwartouw's case only 73%, of the total nitrogen is accounted for by glucosamine. Direct experiment showed that this " extra " nitrogen was not liberated as ammonia or as elementary nitrogen (cf. macrozamin; Langley, Lythgoe, and Riggs, *J.*, 1951, 2309) on acid hydrolysis. It seems quite probable that this extra nitrogen is polypeptide in nature, as in the human blood-group A substance (Aminoff, Morgan, and Watkins, *Biochem. J.*, 1950, **46**, 426); the discrepancy in our case would be accounted for by 6% of a mixture of amino-acids with a mean nitrogen content of 16% and such a quantity might well have been undetectable in our chromatographic experiments. Confirmation of this view was obtained by repeated reprecipitation of a fresh supply of the crude polysaccharide; in this way we were able to obtain a small amount of a polysaccharide (II_3) containing only galactose and glucosamine, in which 93% of the nitrogen was accounted for as glucosamine; the glucosamine content of this preparation was rather low (27%) and the quantity available was insufficient for further investigation.

It is well known that there are close serological relations between the glucosamine-containing polysaccharide of *B. anthracis* and those of type XIV pneumococci, the Forsmann antigen, and the various blood-group substances (for references see Stacey, *Adv. Carbohydrate Chem.*, 1946, **2**, 162; Bray and Stacey, *ibid.*, 1949, **4**, 37; Kabat, *Bacteriol. Reviews*, 1949, **13**, 189), but no detailed discussion of the chemical basis of these relations is possible until further structural investigations have been carried out. It does, however, seem desirable at this stage to draw attention to the relatively low glucosamine content of our polysaccharide II, to the fact that this substance differs from the A (Aminoff and Morgan, *Biochem. J.*, 1951, **48**, 74), B (Gibbons and Morgan, *ibid.*, 1954, **57**, 283), Lewis (Annison and Morgan, *ibid.*, 1952, **50**, 460), and H (*idem*, *ibid.*, 1952, **52**, 247) blood-group substances in being devoid of chondrosamine, and to the very marked difference in optical rotatory power between the anthrax polysaccharide ($[\alpha]_D$ +61°) and the others ($[\alpha]_D$ within the range −40° to +20°).

Experimental

Isolation of Crude Polysaccharide.—Two strains of *B. anthracis* were used, *viz.*, the highly virulent " Vollum " strain, grown under conditions not leading to marked capsule formation, and the avirulent, non-capsulated " Weybridge " strain; further details are given by Gladstone (*Brit. J. Exp. Path.*, 1946, **27**, 394) and by Hanby and Rydon (*loc. cit.*).

The isolation procedures were controlled serologically with anti-sera prepared in rabbits against the two strains; no significant difference was encountered between the two anti-sera in their capacity for precipitating the polysaccharide.

Preliminary experiments showed that little or no serologically active polysaccharide could

be extracted, by a variety of methods, from washed suspensions of cultures grown on CCY-agar (Gladstone and Fildes, *Brit. J. Exp. Path.*, 1940, **21**, 161). It was thought that this failure might be due to liberation, and consequent loss, of the polysaccharide during the extensive autolysis which accompanies washing and this was confirmed by the successful isolation of active material by alcohol precipitation of Seitz filtrates of bacterial suspensions autolysed at 45° for 2 days; it was later found preferable to grow the organisms on liquid CCY (Gladstone and Fildes, *loc. cit.*). It was also found that considerable amounts of active polysaccharide were present in the culture fluid; since the volume of this is so much greater than that of the corresponding amount of autolysate it proved convenient, for bulk preparation, to discard the bacteria and to isolate the polysaccharide from the culture filtrate alone.

Details of the final procedures are given below. The average yield of crude polysaccharide was 500 mg. from 1 l. of autolysate and 200 mg. from 1 l. of culture fluid. The crude material gave precipitates with the rabbit anti-sera at dilutions down to about 1 in 32×10^4; there was no marked difference in serological activity between preparations from the two strains or between preparations from autolysed cells or culture fluid.

(a) *From lysed organisms.* Organisms grown on liquid CCY or on CCY-agar (Gladstone and Fildes, *loc. cit.*) were suspended in water to a creamy consistency and allowed to autolyse at 45° for 2 days. The bacterial bodies were then removed by centrifugation and the supernatant liquid Seitz-filtered; the filtrate was treated with 3 vols. of ethanol and kept at 2° overnight. The precipitate was collected by centrifugation, dissolved in water, and dialysed for 2 days against running tap-water and then for 3 days against frequent changes of distilled water. The product was then concentrated to small bulk under reduced pressure at room temperature; at this stage the biuret test was negative. The solution was treated with 4 vols. of ethanol and kept for some hours; the precipitate was collected by centrifugation, washed with absolute ethanol, and dried *in vacuo* over phosphoric oxide. The product was a light brown powder which was serologically active against the rabbit anti-sera; some properties of materials prepared in this way are given in Table 1 (B1—F16).

(b) *From culture filtrate.* The organisms were grown on liquid CCY, and the bacterial bodies precipitated by the addition of a little acid; the supernatant fluid was decanted through a Seitz filter and the filtrate concentrated under reduced pressure at 35—40° to about one-tenth of its original volume. Crude polysaccharide was precipitated from the concentrate by the addition of 3 vols. of ethanol and collected by centrifugation after being kept overnight at 2°. This product was dissolved in water and dialysed for 2 days against running tap-water and then for 3 days against frequent changes of distilled water. The product was again concentrated under reduced pressure (to about 1/40 of the original volume), precipitated with 3 vols. of ethanol, kept overnight at 2° after the addition of one drop of acetic acid, centrifuged, washed with absolute ethanol, and dried *in vacuo* over phosphoric oxide. The products were serologically active, light brown powders; some of their properties are recorded in Table 1 (F18—F50).

TABLE 1. *Crude polysaccharide from B. anthracis.*

Prep. no.	Strain	Source	N (%)	$[\alpha]_D$	Titre against rabbit anti-serum	Yield (mg./l.)
B1	Weybridge	Autolysate	—	—	—	5280
F11A	Vollum	,,	3·3	+63°	—	380
F13	Weybridge	,,	—	+47	$1:16 \times 10^4$	520
F16	Vollum	,,	—	—	$1:16 \times 10^4$	445
F18	Vollum	Culture filtrate	2·6	+22	$1:64 \times 10^4$	83
F19	Weybridge	,,	4·0	+32	$1:32 \times 10^4$	119
F28X	Weybridge	,,	—	—	—	123
F29X	Vollum	,,	—	—	—	288
F30	Vollum	,,	—	—	$1:32 \times 10^4$	60
F39X	Vollum	,,	—	—	—	224
F48	Vollum	,,	—	—	$1:32 \times 10^4$	144
F50	Weybridge	,,	—	—	$1:16 \times 10^4$	124

Separation of the Two Polysaccharides.—The following are the details of a typical preparation:

The crude polysaccharide (F50) (14·89 g.) was dissolved in water (300 ml.), and a small insoluble residue filtered off and rejected. To the clear brown solution saturated barium hydroxide solution (260 ml.) was added, this amount being sufficient to produce complete precipitation. After 30 min. at 5°, the precipitate was collected by centrifugation and dissolved in 4% acetic acid (125 ml.), and a small insoluble residue was removed by centrifugation. The clear brown solution was dialysed at 2° against frequent changes of distilled water until free

from barium and acetate ions (3 days). The solution was then concentrated under reduced pressure at room temperature and finally dried from the frozen state. The product (F50A) was a pale buff solid; the yield of polysaccharide I was 2·250 g.

The supernatant liquid from the barium hydroxide precipitation was treated with carbon dioxide to remove barium ions, the barium carbonate filtered off, and the filtrate made 5% with respect to sodium acetate (trihydrate) and 2% with respect to acetic acid and then treated with 3 vols. of ethanol. After being kept overnight at 2°, the supernatant liquid was decanted off and the precipitate dissolved in water and dialysed at 2° against frequent changes of distilled water until free from acetate ion (4 days). Concentration and drying from the frozen state gave 2·918 g. of polysaccharide II (F50B).

The results of a number of separations by this procedure are summarised in Table 2.

TABLE 2. *Separation of polysaccharides I and II.*

	Polysaccharide I					Polysaccharide II				
Starting material	Prep. no.	N (%)	$[\alpha]_D$	Titre against rabbit anti-serum	Yield (%)	Prep. no.	N (%)	$[\alpha]_D$	Titre against rabbit anti-serum	Yield (%)
F13	F13A	1·9	+45°	$1:128 \times 10^4$	2·1	F14	4·1	+66°	0	38·5
F16	F16A	3·85	+44	$1:32 \times 10^4$	9·9	F17	4·2	+69	0	23·0
F18	F18A	2·1	+38	$1:256 \times 10^4$	15·5	F18C	4·5	+30	$1:32 \times 10^4$	15·0
F19	F19A	2·6	+41	$1:256 \times 10^4$	11·4	F19C	4·5	+51	0	28·0
F28X	F28A	—	—	$1:256 \times 10^4$	8·0	F28C	—	—	$1:32 \times 10^4$	20·5
F29X	F29A	—	—	$1:256 \times 10^4$	2·9	F29C	—	—	0	26·7
F48	F48A	—	—	$1:256 \times 10^4$	11·1	F48B	—	—	0	14·5
F50	F50A	—	—	$1:256 \times 10^4$	15·1	F50B	—	—	0	19·6
F30	F40	—	—	$1:128 \times 10^4$	11·0	—	—	—	—	—

Polysaccharide I.—(a) *Purification.* The partly purified polysaccharide F50A (2·24 g.) was dissolved in water (70 ml.) and treated with saturated barium hydroxide solution (70 ml.). After 45 min. at 2°, the precipitate was collected by centrifugation, dissolved in 4% acetic acid (20 ml.), and dialysed against distilled water until free from barium and acetate ions. The solution was then concentrated at room temperature under reduced pressure and finally dried from the frozen state. The product, F50C (720 mg.), was an almost colourless porous mass which dissolved readily and completely in water; it had $[\alpha]_D^{19}$ +72·6° (*c* 1·5 in H_2O) and gave a precipitate with the Weybridge rabbit anti-serum at dilutions down to $1:512 \times 10^4$; this material was used for most of the analytical work. A similar purification of F48A (960 mg.) gave F48C (500 mg.) with $[\alpha]_D^{23}$ +69·7° (*c* 1·5 in H_2O), active at $1:256 \times 10^4$. Elementary analyses of these two materials gave the following results :

	C (%)	H (%)	N (%)	P (%)	Ash (%)
F48C	35·7	7·8	0·7	—	4·43
F50C	36·8	7·5	0·5	—	3·3
	37·6	6·8	1·1	0·87	3·3

(b) *Reducing power before and after hydrolysis.* Solutions of the polysaccharide in 0·5N-hydrochloric acid (*ca.* 1 mg./ml.) were heated at 100° in sealed tubes for various times. The tubes were cooled and the contents accurately neutralised with sodium carbonate and made up to 10 ml. with water. The reducing power was then determined by Hagedorn and Jensen's method (*loc. cit.*) with the following results :

Time (hr.)		0	1	2	3	3·5	4	5	6	18	21	72
Reducing value as glucose, %	F48C	2·6	26·1	38·5	72·4	81·5	86·1	90·5	90·5, 91·3	86·8	84·5	48·0
	F50C	—	—	—	—	—	—	—	91·3	—	—	—

(c) *Paper chromatography of hydrolysate.* The polysaccharide F50C (50 mg.) was hydrolysed for 6 hr. at 100° in a sealed tube with 0·5N-sulphuric acid. Sulphate ions were removed with barium hydroxide and the supernatant liquid from the barium sulphate was evaporated to dryness and made up to 2·5 ml. with water.

One-dimensional chromatograms were run on Whatman No. 1 filter paper, with both phenol and collidine for development and ammoniacal silver nitrate as the spraying reagent (Partridge, *Biochem. J.*, 1948, **42**, 238). Only one spot appeared with either solvent. That obtained with phenol had R_F 0·48, controls on the same paper giving the following R_F values : galactose, 0·44; mannose, 0·48; fructose, 0·56; glucosamine, 0·69 (Partridge, *loc. cit.*, gives 0·44, 0·45, 0·51, and 0·62 respectively). With collidine, the spot given by the hydrolysate had R_F 0·58;

controls gave the following R_F values: galactose, 0·52; fructose, 0·55; mannose, 0·58 (Partridge, *loc. cit.*, gives 0·34, 0·42, and 0·46 respectively, but the variability of commercial collidine is well-known, cf. Dent, *Biochem. J.*, 1948, **43**, 169). Control experiments showed the monosaccharide from the hydrolysate to be easily separable from added fructose but inseparable from mannose.

(d) *Estimation of mannose.* The following procedure was used: 1 ml. of solution, containing 0·1—0·2 mg. of mannose, was added to 9 ml. of 8 : 1 (by vol.) concentrated sulphuric acid–water, with ice-cooling; 0·3 ml. of a 0·5% solution of carbazole (purified as described by Gurin and Hood, *loc. cit.*) in ethanol was then added. After thorough mixing, the solution was heated in a boiling-water bath for 10 min., then cooled and the colour read on the Spekker absorptiometer, a 1-cm. cell and Ilford Spectrum Green Filter No. 604 being used. The reference curves was linear, 0·2 mg. of mannose giving a reading of 0·230.

F50C was hydrolysed with 0·5N-sulphuric acid at 100° for 6 hr.; duplicate analyses gave mannose yields of 98·5 and 98·6%.

(e) *Isolation of mannose methylphenylhydrazone.*—F50C (20 mg.) was hydrolysed for 6 hr. at 100° in a sealed tube with 0·5N-sulphuric acid. The cooled product was exactly neutralised with barium hydroxide solution, barium sulphate removed by centrifugation, and the supernatant liquid concentrated under reduced pressure to a syrup. 1 ml. of a 25% solution of *N*-methyl-*N*-phenylhydrazine in ethanol containing 3% of acetic acid was added and the mixture kept at 30° for 1 hr. and then at 0° for 20 min. The crystals which separated on scratching were filtered off, washed, and recrystallised from 70% ethanol; the product (10 mg.) had m. p. 179°, not depressed on admixture with an authentic specimen of D-mannose *N*-methyl-*N*-phenylhydrazone, m. p. 179° (lit., m. p. 181°).

(f) *Oxidation with periodic acid.* F50C (16·2 mg.) was dissolved in water (10 ml.); 1-ml. portions of this solution were kept at room temperature with 0·00548N-sodium periodate (5 ml.) and acetate buffer of pH 5·2 (0·5 ml.). The results, expressed in terms of monosaccharide units of mol. wt. 197, being hexose units corrected * for hydration on the basis of the observed reducing power, were as follows:

Time (hr.)	1	3·5	6	1·5	23·5	4·6
Mols. periodate consumed per monosaccharide unit...	0·13	0·59	0·85	1·02	1·11	1·14

(g) *Methylation.* F50C (100 mg.), dissolved in water (2 ml.) and 35% sodium hydroxide solution (3 ml.), was stirred under nitrogen while methyl sulphate (1·5 ml.) was added dropwise (1 drop per hr.). After the addition was complete the temperature was raised to 100° and stirring continued for 1 hr. Extraction of the acidified solution with chloroform yielded only 15 mg. of an incompletely methylated product (Found: OMe, 22·7%). This was dissolved in acetone (5 ml.) and added to the solution previously extracted with chloroform. Sodium hydroxide solution (35%; 14 ml.) was added and the mixture shaken under nitrogen while methyl sulphate (8·5 ml.) was added dropwise (2 drops per min.). When the addition was complete, acetone (10 ml.) was added and the solution was refluxed for 1 hr. The cooled solution was acidified with 0·5N-sulphuric acid and cooled to 0°; the sodium sulphate which separated was removed by filtration and washed with acetone (10 ml.). The washings were added to the filtrate which was then again subjected to the methylation procedure. After fifteen methylations the final acidified solution was evaporated under reduced pressure to 200 ml. and kept for some hours at 0°. Sodium sulphate was removed by filtration, and both it and the filtrate were thoroughly extracted with chloroform. Evaporation of the dried extract and washing of the residue with light petroleum (b. p. 40—60°) yielded 20 mg. of methylation product.

This was refluxed overnight with 1% methanolic hydrogen chloride (10 ml.); the solution was evaporated to dryness under reduced pressure and then heated at 100° for 6 hr with 0·5N-hydrochloric acid (10 ml.). Silver carbonate (1 g.) was added and the solution filtered; some residual silver ions were removed by hydrogen sulphide and filtration. Finally, the solution was neutralised with barium carbonate and evaporated to dryness under reduced pressure. The crude product, on paper chromatography by the method of Hirst, Hough, and Jones (*J.*, 1949, 931), with butan-1-ol–ethanol–water as developing liquid and tetra-*O*-methyl-D-glucose as reference sugar, gave two spots of R_G 0·895 and 0·745 respectively.

Distillation gave a crystalline (b. p. 80°/0·5 mm.) and an amorphous (b. p. 100°/0·5 mm.) product; the former had m. p. 93—97°.

* The correction is made as follows. A polyhexose should give 111% of hexose on hydrolysis; F50C gave only 91%. The discrepancy is ascribed to hydration and the mol. wt. of the hydrated hexose unit is $162 \times 111/91 = 197$.

The hydrolysis product was boiled under reflux for 1 hr. with aniline (10 mg.) in ethanol (10 ml.); on evaporation followed by addition of one drop of ether, the product crystallised in needles, m. p. 118°. Two sublimations at 110°/0·005 mm. yielded 2 : 3 : 6-tri-*O*-methyl-D-mannosylaniline, m. p. 127°, mixed m. p. with an authentic specimen (m. p. 129°) 128°.

Polysaccharide II.—(a) *Purification.* Mixed, weakly serologically active fractions (5·27 g.) from both Vollum and Weybridge strains were dissolved in water (76 ml.) and treated with sufficient saturated barium hydroxide solution (40 ml.) to give complete precipitation. The precipitate was removed by centrifugation and the supernatant liquid freed from barium ions with carbon dioxide. The barium carbonate was filtered off and the completely inactive preparations F50B and F39 (3·39 g. in all) were dissolved in the filtrate. Polysaccharide was precipitated from this solution, which had been made 5% with respect to sodium acetate and 2% with respect to acetic acid, by addition of 3 vols. of ethanol. The precipitate was collected by centrifugation after being kept at 2° overnight, then dissolved in water (50 ml.), and the whole procedure was twice repeated. The final product was dissolved in water, dialysed, concentrated, and dried from the frozen state. The product, F51 (5·295 g.), gave only a trace of precipitate with the Weybridge rabbit anti-serum at a dilution of $1 : 16 \times 10^4$ and had $[\alpha]_D^{22} +61·5°$ (*c* 1·5 in H_2O).

This material was further purified by dissolving it (4·5 g.) in water (45 ml.) and treating this with saturated barium hydroxide solution (20 ml.); no precipitate appeared even overnight at 2°. The bulk of the barium ions were removed by carbon dioxide, and the remainder, after removal of the barium carbonate by filtration, by the addition of the necessary amount of 2N-sulphuric acid (0·3 ml.). Barium sulphate was removed by centrifugation and sodium acetate trihydrate (2·0 g.) and acetic acid (0·8 ml.) were dissolved in the supernatant liquid; ethanol (120 ml.) was added and the mixture kept at 2° overnight. The supernatant liquid was poured off and the sticky residue dissolved in water (40 ml.) and again precipitated with ethanol (120 ml.). The final precipitate was dissolved in water and dialysed at 2° against frequent changes of distilled water. The dialysed solution (71 ml.) was diluted to 200 ml. and dried from the frozen state. The product, R926D (3·6 g.), was a pale cream-coloured spongy mass which was readily and completely soluble in water; it gave only a trace of precipitate with the Weybridge rabbit anti-serum at a dilution of $1 : 8 \times 10^4$ and had $[\alpha]_D^{20} +61·0°$ (*c* 1·0 in H_2O). The results of elementary analyses of F51 and R926D were as follows:

	C (%)	H (%)	N (%) *	Acetyl (%)	Loss of wt. at 100° (%)	Ash (%)
F51	40·0	6·8	4·0 (K)	—	—	0·9
R926D ...	39·0	7·1	3·0 (D), 3·4 (K)	7·3	—	0·0
	39·9	7·0	3·2 (D)	6·6	1·2	0·0
	38·4	7·3	3·6, 3·4 (K)	—	2·2	0·0

* D = Dumas; K = Kjeldahl.

Repeated application of the baryta precipitation procedure to a further 10 g. of crude polysaccharide yielded 80 mg. of a specimen (II_3) of polysaccharide II in which 93% of the nitrogen was accounted for as glucosamine. This product had $[\alpha]_D^{20} +62·0°$ ($c = 1$ in H_2O) and a reducing value after hydrolysis (method of Fairbridge, Willis, and Booth, *loc. cit.*) of 100%, and gave 27·0% of glucosamine (estimated by the method of Palmer, Smythe, and Mayer, *loc. cit.*) on hydrolysis.

TABLE 3. *Hydrolysis of polysaccharide II.*

(a) *Analysis by Hagedorn and Jensen's method*; F51.

Time (hr.)	4	5	6	16	21	48
Reducing value as glucose (%)	65·5	66·3	68·4	67·5	37·0	32·0
Yield of 2 : 1 galactose : glucosamine (%) ...	76·7	77·6	80·1	79·1	43·3	37·5

(b) *Analysis by Jendrassik and Polgar's method.*

Time (hr.)		2	4	6
Reducing value as glucose (%)	R926D	54·5	60·8	64·5
	Galactose	77·5	69·5	59·2
	Glucosamine	97·8	94·0	90·5
Yield of 2 : 1 galactose : glucosamine (%) ...		64·7	78·3	92·7

(b) *Reducing power before and after hydrolysis.* In the first series of experiments the hydrolysis was conducted as described (p. 3870) for polysaccharide I and the reducing power determined by Hagedorn and Jensen's method (*loc. cit.*); the results, corrected for the known Hagedorn–Jensen reducing powers of galactose (132 mg. equiv. to 100 mg. of glucose; Sobotka and Reiner, *Biochem. J.*, 1930, **24**, 394) and glucosamine (95 mg. equiv. to 100 mg. of glucose; Ivánovics, *Z. Immunitäts.*, 1940, **97**, 402), are given in Table 3(a).

In the second series of experiments the hydrolyses were conducted similarly and the reducing power determined by Jendrassik and Polgar's method (*Biochem. Z.*, 1940, **304**, 271); correction was made for the not inconsiderable decomposition of galactose and glucosamine by carrying out simultaneous "hydrolyses" with these two monosaccharides; the results are shown in Table 3(b).

In another series of experiments the reducing value was determined colorimetrically with triphenyltetrazolium chloride (cf. Fairbridge, Willis, and Booth, *loc. cit.*). Solutions (1 ml.) of the polysaccharide and of galactose and glucosamine (all 0·50 mg./ml.) were mixed with 2N-hydrochloric acid (0·5 ml.) and heated at 100° in sealed tubes for 6 hr.; the tubes were then opened, treated with N-sodium hydroxide (2 ml.) and 1% aqueous triphenyltetrazolium chloride (0·5 ml.), and heated in a vigorously boiling water-bath for 3 min. 1·1N-Acetic acid (1 ml.) was added to the cooled solutions, and the mixture diluted to 10 ml. with aldehyde-free *iso*propyl alcohol (distilled from *m*-phenylenediamine); 1 ml. of this solution was made up to 10 ml. with the same *iso*propyl alcohol and the colour read on the Spekker absorptiometer, an Ilford Spectrum Blue Filter No. 602 and a 1-cm. cell being used. Under these conditions both galactose and glucosamine give identical linear reference curves; the actual colour value is very sensitive to slight changes in conditions and it was for this reason that parallel experiments were performed with the two sugars. Another similar series of tubes was set up with the hydrochloric acid replaced by water and without heating. The results indicated a reducing value of 2·3% (as hexose) before hydrolysis and 93·5% after hydrolysis.

(c) *Paper chromatography of hydrolysate.* The polysaccharide, R926D (50 mg.), was hydrolysed for 6 hr. at 100° with 0·5N-sulphuric acid. Sulphate ions were removed with aqueous barium hydroxide, and the supernatant liquid from the centrifuged sulphate was evaporated to dryness and dissolved in water (2·5 ml.). One-dimensional paper chromatograms were run on Whatman No. 1 filter paper, with both phenol and collidine as developing solvents, with ammoniacal silver nitrate as the spraying reagent (Partridge, *loc. cit.*). With phenol, two spots were obtained with R_F values of 0·42 and 0·65; reference specimens of galactose and glucosamine run simultaneously on the same sheet gave R_F values of 0·42 and 0·65 (Partridge, *loc. cit.*, gives 0·44 and 0·62). Our sample of collidine failed to separate the two sugars, giving only a single spot with R_F 0·52—0·53; Partridge (*loc cit.*) gives R_F values of 0·30 and 0·43 for glucosamine and galactose, respectively, but the variability of commercial collidine is well known (cf. Dent, *loc. cit.*).

In experiments designed to identify the hexosamine, the polysaccharide was hydrolysed, as usual, with 0·5N-hydrochloric acid at 100° for 6 hr. and the hydrolysate evaporated to dryness *in vacuo* over sodium hydroxide. Chromatograms were run one-dimensionally with phenol and collidine on Whatman No. 1 paper and sprayed with Moore and Stein's ninhydrin reagent (*J. Biol. Chem.*, 1948, **176**, 367); only a single spot was obtained, showing the absence of amino-acids and other primary amines. Comparative runs with the hydrolysate and authentic specimens of glucosamine and chondrosamine hydrochloride showed the hexosamine in the hydrolysate to be chromatographically identical with glucosamine; glucosamine moves faster than chondrosamine in collidine and more slowly in phenol, and the hexosamine in the hydrolysate was readily separated on the paper from added chondrosamine but inseparable from added glucosamine.

(d) *Isolation of glucosamine derivatives.* The polysaccharide, R926D (120 mg.), was refluxed for 5 hr. with 5N-hydrochloric acid (10 ml.); humin was removed by filtration through asbestos and the filtrate steam-distilled to remove volatile decomposition products. The residual solution was boiled with charcoal, filtered, concentrated to 1 ml., and kept overnight at 0°. Large crystals of D-glucosamine hydrochloride (40 mg.; 28% as glucosamine) separated and were recrystallised from hot water (0·5 ml.). The product had $[\alpha]_D^{20}$ + 76·0° (*c* 1·0 in H_2O) (lit., +72·5°) and gave an *X*-ray powder photograph indistinguishable from that given by authentic D-glucosamine and quite different from that given by authentic D-chondrosamine. Paper chromatography of the crude hydrochloride and of the filtrate revealed no ninhydrin-reacting material other than glucosamine.

A portion of the crude hydrochloride (15 mg.) was dissolved in water (1 ml.), and the solution thoroughly mixed with 2 : 4-dinitrofluorobenzene (0·01 ml.) in ethanol (2 ml.); N-sodium carbonate (0·01 ml.) was added and the mixture shaken for 1 hr. The ethanol was then removed under reduced pressure and the aqueous residue extracted continuously with ether for 12 hr. The extract was dried (Na_2SO_4) and evaporated; addition of a few drops of chloroform to a solution of the residue in acetone (0·5 ml.) gave a crystalline precipitate of *N*-2 : 4-dinitrophenyl-D-glucosamine, m. p. 197—200° (Found: C, 41·75; H, 4·9. Calc. for $C_{12}H_{15}O_9N_3$: C, 41·7;

H, 4·3%); there was no depression of m. p. on admixture with an authentic specimen, m. p. 200° [Annison, James, and Morgan, *Biochem. J.*, 1951, **48**, 477, give m. p. 202—204° (corr.)].

(e) *Isolation of galactose methylphenylhydrazone.* The polysaccharide, R926D (80 mg.), was heated with 0·5N-hydrochloric acid (2 ml.) at 100° in a sealed tube for 6 hr. The hydrolysate was cautiously neutralised with sodium carbonate (53 mg.) and warmed to expel carbon dioxide. A 25% alcoholic solution (2 ml.) of *N*-methyl-*N*-phenylhydrazine, containing a few drops of acetic acid, was added and the mixture kept at 30° for 1 hr. The product was cooled in ice and filtered and the crystals were washed with ethanol and recrystallised from the same solvent. The product (50 mg., 40% as galactose) had m. p. 188°, not depressed on admixture with authentic D-galactose *N*-methyl-*N*-phenylhydrazone, m. p. 189° (lit., m. p. 191°).

(f) *Estimation of galactose.* The procedure was identical with that used for the estimation of mannose (p. 3871). The reference curve was linear and passed through the origin; 0·40 mg. of galactose gave a Spekker reading of 0·490; glucosamine gave a negligible colour. Hydrolyses were carried out in the usual manner with 0·5N-sulphuric acid; the results were as follows:

Time (hr.)	1·17	2	3	4	6	25
Galactose (%)	60	62	60	59	57	37

(g) *Estimation of glucosamine.* (i) Method of Palmer, Smyth, and Meyer. The hydrolyses were carried out at 100° in the usual manner. The colours were measured on the Spekker absorptiometer with 1 cm. cells and Ilford Spectrum Green Filter No. 604; the reference curve was linear and passed through the origin, 100 g. of glucosamine giving a reading of 0·400. The results are recorded in Table 4; no detectable glucosamine was liberated after 22·5 hours' heating with N-acetic acid at 100°.

(ii) Tracey's method. The hydrolysate (*ca.* 1 mg./ml.) was distilled with saturated trisodium phosphate solution, saturated with sodium borate, in a Markham apparatus (*Biochem. J.*, 1942, **36**, 790) and the ammonia collected in 2% boric acid and estimated colorimetrically with Nessler's reagent (Ilford Spectrum Violet Filter No. 601). The results are recorded in Table 4.

TABLE 4. *Liberation of glucosamine from polysaccharide II on hydrolysis.*

Time (hr.)			1·25	1·5	2·5	3·75	4·0	4·5	6·0	8·0	22
Glucosamine liberated (%)	with 0·5N-HCl	(*a*)	12·7	—	24·3	27·3	—	—	29·3	29·0	28·3
		(*b*)	—	16·6	17·6	—	25·6	—	33·4	—	33·2
	with 6N-HCl	(*a*)	—	—	28·9	32·7	—	—	31·0	29·2	—

(*a*) Glucosamine determined by the method of Palmer, Smyth, and Meyer. (*b*) Glucosamine determined by Tracey's method.

(h) *Oxidation with periodic acid.* R926D was oxidised as described above for F50C (p. 3871). The results, calculated for a monosaccharide unit of mol. wt. 193 (cf. p. 3871), were as follows:

Time (hr.)	1	4	8	17	24	40
Periodate (mol.) consumed per monosaccharide unit ...	0·455	0·515	0·61	0·665	0·715	0·74

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The Fluorescence Spectra of Coronene and 1 : 12-Benzoperylene at Low Temperatures.

By E. J. Bowen and B. Brocklehurst.

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The fluorescence spectra of coronene and 1 : 12-benzoperylene in hydrocarbon glasses at about −180° are reported. In light petroleum the spectra consist of series of sharp bands in the violet and blue. In hexane and heptane, further splitting of some of the bands occurs. Specific solvent effects seem to be involved.

The fluorescence spectrum of coronene (I) has been studied by Shpol'skii, Il'ina, and Klimova (*Doklady Akad. Nauk S.S.S.R.*, 1952, **87**, 935). They reported that, in organic solvents, it consists of a series of narrow bands in the violet and blue. When the solutions are cooled with liquid air, the bands become very narrow—much more so than those of most other aromatic hydrocarbons. In particular, in frozen hexane and heptane, there is further splitting of the bands into very fine "lines," of which more than eighty were detected by photography.

(I) (II)

The present work confirms these results in general, but it is shown that the coronene used by the Russian workers must have contained an impurity, and that the spectrum studied was that of two substances. The coronene used by us had been separated from the by-products of the hydrogenation of coal, by repeated fractional crystallisation. Even after further purification by chromatography on alumina, it was found that the fluorescence spectrum varied with the wave-length of the exciting light; there were also small differences in the absorption spectrum in the range 3500—4000 Å. The impurity responsible for this effect can be partly removed and concentrated by repeated vacuum-distillations, and appears from its absorption spectrum to be 1 : 12-benzoperylene (II) (Clar, "Aromatische Kohlenwasserstoffe," Springer, Berlin, 1941). Absorption measurements show that the original coronene contained about 6% of benzoperylene, and fractions were finally obtained containing less than 1% and about 40%. Further purification of the benzoperylene was not attempted for this work as the two substances absorb selectively at different wave-lengths. The molar extinction coefficients at 3650 and 3135 Å are: coronene, 320 and 32,000; benzoperylene, 23,000 and 7500. Although the coronene used by the Russian workers contained very little benzoperylene, their excitation by 3650 Å light exaggerated the benzoperylene fluorescence from the material. Our results are for our purest coronene excited at 3135 Å, and for the specimen containing 40% of benzoperylene excited at 3650 Å. In each case there was no detectable fluorescence from the other substance. The two separate spectra, taken together, include nearly all the peaks obtained by the Russians.

Experimental

A high-pressure mercury lamp with a clear glass envelope was used with a Chance OX 1 glass filter as a source of 3650 Å light. Light of wave-length 3135 Å was obtained from a similar lamp from which the envelope had been removed; Chance OX 7 glass and a solution of nickel, cobalt, and copper sulphates were used as filters. The optical arrangements are shown in Fig. 1: the light from the lamp (*A*), focused by a lens (*L*), was reflected by a front surface-aluminised mirror (*M*) on to the specimen in a recessed copper disc (*D*); the latter was attached to a copper rod, the lower end of which was immersed in liquid oxygen. Thermal insulation of the specimen was provided by a vacuum-jacket connected to the rod by a copper–glass seal (*C*). The incident and the fluorescent light passed through a silica disc immediately above the

specimen. A copper–constantan thermocouple (*T*) soldered to the side of the copper disc, showed that a temperature of about −180° was reached.

The fluorescent light was reflected by a prism into the slit (*S*) of a Hilger constant-deviation spectrometer with a glass prism. Light from the exit-slit fell on the cathode of a photomultiplier (R.C.A. 931A), the output of which was measured after amplification. The instrument was calibrated with a standard tungsten lamp to enable the results to be plotted as intensities on a quantum basis.

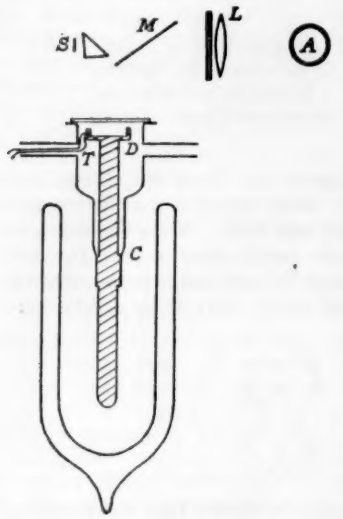


FIG. 1. *Apparatus for the measurement of fluorescence spectra at low temperatures.*

RESULTS AND DISCUSSION

Measurements were made on the fluorescence spectra of coronene in *n*-hexane, *n*-heptane, light petroleum (b. p. 80—100°), liquid paraffin, and ethanol, and of benzoperylene in the first three solvents. In light petroleum the coronene spectrum has twelve sharp peaks; in heptane, five of these split into doublets, the peaks of which are separated by 60—70 cm.$^{-1}$, and two new weak peaks appear. The spectrum in hexane is similar, but the doublets are less sharply resolved. The wave-lengths of the peaks in hexane and heptane are identical within the experimental error, but both are shifted to the red relative to the light petroleum solution, by about 40 cm.$^{-1}$. In alcohol, the spectrum is practically identical, in position and structure, with that in light petroleum. Liquid paraffin gives similar results, but the spectrum is somewhat more diffuse.

1 : 12-Benzoperylene in light petroleum has a relatively diffuse fluorescence spectrum. This becomes sharper in heptane, and, unlike the coronene spectrum, sharper still in hexane. The peaks do not shift appreciably on change of solvent. The peak at 4450 Å coincides with the main peak of coronene, but its relative intensity is the same in mixtures containing more coronene so it is very probably due to the benzoperylene.

Coronene, in solution at low temperatures, has a strong yellow phosphorescence which has a lifetime of several seconds. The low sensitivity of the photomultiplier to yellow light prevented us from obtaining significant measurements. The phosphorescence spectrum has been recorded by Shopl'skii and his co-workers (*loc. cit.*); it has a very sharp structure, and there are distinct differences between hexane and heptane solutions. Benzoperylene has no detectable afterglow, and its presence as an impurity does not therefore interfere with their results in this wave-length region.

The first singlet–singlet transition of coronene is probably forbidden by symmetry (Brocklehurst, *J.*, 1953, 3318), but becomes weakly allowed by coupling with unsymmetrical vibrations, as in the case of benzene (see, *e.g.*, Sponer, Nordheim, Sklar, and Teller, *J. Chem. Phys.*, 1939, **7**, 207). There is then the possibility of further combination with symmetrical vibrations, as in the case of allowed transitions (Franck–Condon principle). At liquid-oxygen temperature, only vibrations of the ground state need be considered. In the spectrum obtained from light petroleum solution, there are four series of three bands, *i.e.*, four different unsymmetrical vibrations must be involved. The magnitudes of these quanta cannot be measured as the position of the 0–0 line is uncertain. The symmetrical vibration is the same in all four series, as they all show inter-peak distances of approximately 1330 cm.$^{-1}$. The spectra in hexane and heptane can be interpreted similarly, doublets only occurring in two of the four series. The spectrum of benzoperylene is more complicated: this is surprising as the transition is not forbidden (as is shown, for example, by the strength of the first absorption band).

The doublets in the spectrum of coronene in hexane and heptane, and the shift of the spectrum relative to light petroleum, are very remarkable. The bands in light petroleum

FIG. 2. *Fluorescence spectrum of coronene in heptane at* −180°. *Peak wave-lengths given in* Å.

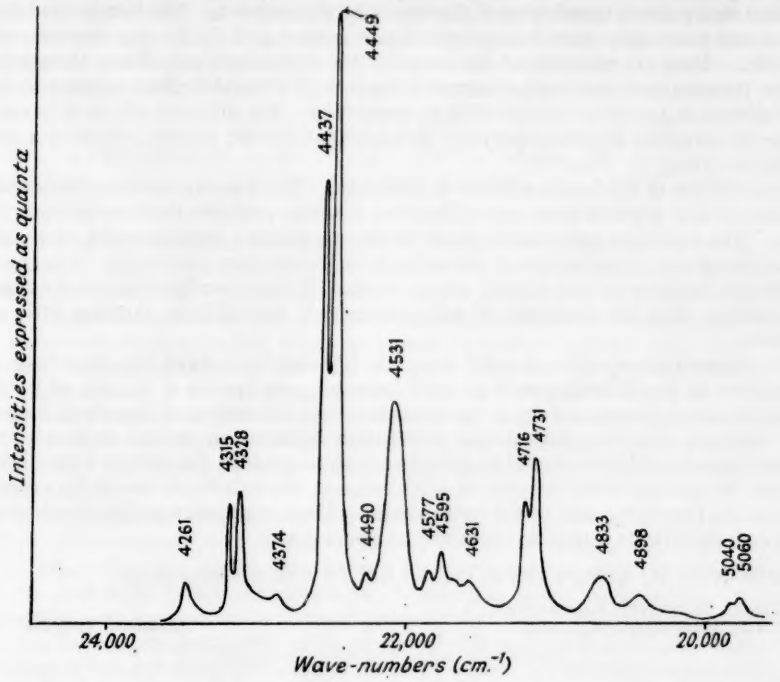
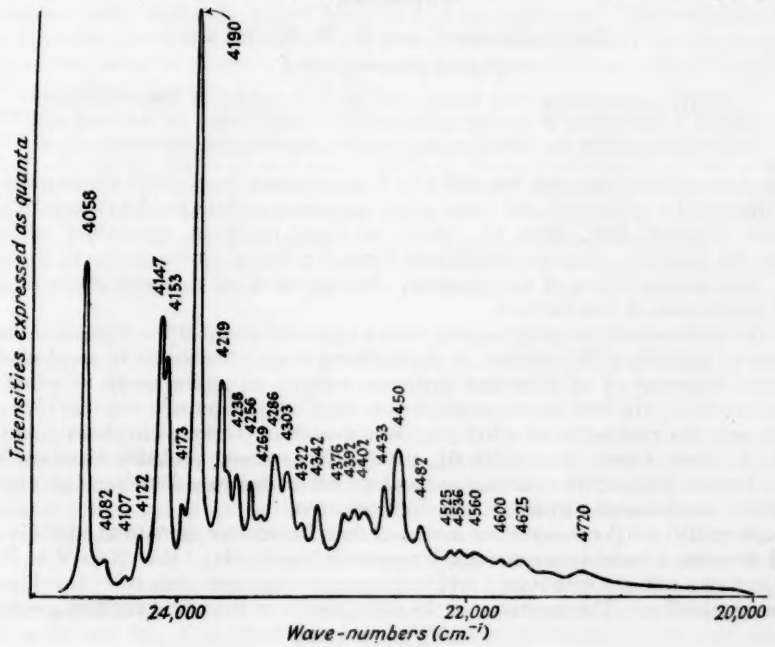


FIG. 3. *Fluorescence spectrum of* 1 : 12-*benzoperylene in hexane at* −180°. *Peak wave-lengths given in* Å.



are as sharp as those in hexane or heptane, and it seems that the lack of doublet structure is not due to a general broadening of the bands by this solvent. The hexane and heptane used are not chemically pure but are petroleum fractions (B.D.H.), free from fluorescent impurities. They are mixtures of the same nature as the light petroleum, though boiling at lower temperatures and over a narrower range. The doublet effect appears to depend on the solvent in a way not attributable to impurities. The different effects of hexane and heptane on coronene and benzoperylene indicate that specific solvent effects of a peculiar type are involved.

The condition of the frozen solvents is uncertain. The Russian workers considered that their hexane and heptane were crystalline, but it seems probable that our solvents formed glasses. The solutions were cooled very rapidly to prevent crystallisation of the solute, and the chemically mixed nature of the solvents facilitates glass formation. The specimens were always transparent and showed many cracks. It is certain that the solutes remain in true solution, since the spectrum of solid coronene is very diffuse, showing little sign of structure.

The fluorescence spectra of solid aromatic hydrocarbons have fine structure at the temperature of liquid hydrogen (*e.g.*, solid benzene; see Sponer *et al.*, *loc. cit.*). This is believed to result from coupling of the transition with vibrations of the whole lattice. It seems unlikely, however, that similar interaction between an excited molecule and the surrounding solvent lattice would be strong enough to produce the effects found here. In any case, by analogy with the case of solid benzene, the sub-bands would be expected to occur on the long-wave side of the main bands. Their occurrence on the short-wave side only seems to indicate a specific effect on the upper state.

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Cyclic Amidines. Part II. Derivatives of 2-Amino-4-hydroxyquinoline.*

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Ethyl cyanoacetate when heated with an arylammonium arenesulphonate affords a derivative of 2-amino-4-hydroxyquinoline; with an α-substituted ethyl cyanoacetate the corresponding 3-substituted quinolines are obtained.

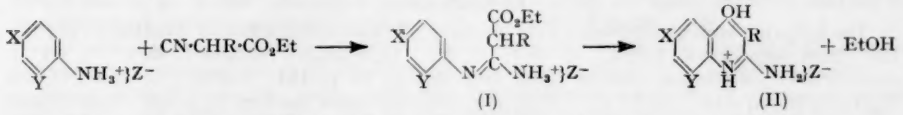
2-AMINO-4-HYDROXYQUINOLINE has hitherto been obtained from ethyl α-cyano-α-*o*-nitrobenzoylacetate by reduction and from ethyl α-cyano-α-*o*-phthalimidobenzoylacetate by hydrolysis (Gabriel, *Ber.*, 1918, **51**, 1500); in these reactions, cyclisation apparently involves the addition of an intermediately formed primary amino-group to the cyano-group. The inaccessibility of the necessary derivatives of ethyl cyanoacetate limits the general application of this method.

For the synthesis of the quinoline ring with a hydroxyl group in the 4-position there are a number of methods which involve, in the cyclising stage, elimination of an alcohol from an alkoxyl fragment of an ester and hydrogen *ortho* to an amino-group attached to an aromatic nucleus; the best known examples are the Conrad–Limpach reaction (*Ber.*, 1887, **20**, 944) and the cyclisation of ethyl β-arylamino-α-ethoxycarbonylacrylates (Gould and Jacobs, *J. Amer. Chem. Soc.*, 1939, **61**, 2890). It appeared probable that an *N*-arylamidine formed from ethyl cyanoacetate and an arylamine would undergo an analogous cyclisation, to a 2-amino-4-hydroxyquinoline derivative.

In agreement, ethyl cyanoacetate and anilinium benzenesulphonate at 210° (1—2 hr.) yielded 2-amino-4-hydroxyquinolinium benzenesulphonate (II; R = X = Y = H, Z = $Ph{\cdot}SO_3$); and a salt of a substituted arylamine gave the appropriately substituted 2-amino-4-hydroxyquinoline. The positions of the substituents in the nine examples given in the

* Part I, *J.*, 1954, 3429.

Experimental section follow from the orientation of the arylamines employed. The production of derivatives of 2-amino-4-hydroxyquinoline having a substituent in the 3-position involved the use of an α-substituted ethyl cyanoacetate; six examples of this are described in the Experimental section. The benzenesulphonate of *p*-nitroaniline and ethyl cyanoacetate reacted violently and none of the desired product was isolated.



(I) (II)

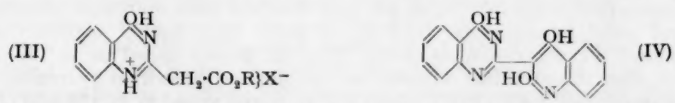
A number of side reactions involving loss of the ethoxycarbonyl group of the cyanoacetate occurred, since acetanilide, *N*-phenylacetamidine, α-cyanoacetanilide, and malondianilide were found amongst the by-products from the preparation of 2-amino-4-hydroxyquinoline. α-Cyanoacetanilide and α-*N*-phenylamidinoacetanilide were formed together with 2-amino-4-hydroxyquinoline when anilinium benzenesulphonate and ethyl cyanoacetate were heated together at 180° for 30 min. However, it appears unlikely that either of these anilides is the significant intermediate in the main reaction, since α-cyanoacetanilide when heated at 210° for an hour with anilinium benzenesulphonate afforded only 4% of 2-amino-4-hydroxyquinoline and 13% of α-*N*-phenylamidinoacetanilide; none of the quinoline was obtained when the benzenesulphonate of α-*N*-phenylamidinoacetanilide was heated.

α-*N*-Phenylamidinoacetanilide was also obtained by interaction of ethyl cyanoacetate and aniline in the presence of aluminium chloride (Oxley, Partridge, and Short, *J.*, 1947, 1110) and when the thio-imidic ester formed by interaction of ethyl cyanoacetate and thioglycollic acid in the presence of hydrogen chloride was heated with aniline. When the latter reaction was carried out at room temperature, α-ethoxycarbonyl-*N*-phenylacetamidine was isolated in small yield as its picrate (I; R = X = Y = H, Z = $C_6H_3O_7N_3$). This compound was not detected amongst the by-products of the reaction between ethyl cyanoacetate and anilinium benzenesulphonate.

ω-Cyanoacetophenone and anilinium benzenesulphonate afforded ω-*N*-phenylamidinoacetophenone (14%) and only 3% of 2-anilino-4-phenylquinoline. The formation of the latter presumably involved a secondary reaction of the intermediately formed 2-amino-4-phenylquinoline with the aniline salt analogous to that known to occur with *N*-phenylbenzamidine (Bernsthen, *Annalen*, 1877, **184**, 354).

Attempts to produce a 3 : 3-disubstituted dihydroquinoline derivative from a disubstituted ethyl cyanoacetate and a salt of an arylamine were unsuccessful; the ethoxycarbonyl group was lost and a derivative of *N*-phenylacetamidine was obtained. Thus ethyl α-benzyl-α-cyano-β-phenylpropionate with anilinium benzenesulphonate or *p*-methoxyanilinium benzenesulphonate furnished 1 : 3-diphenyl-2-*N*-phenylamidinopropane and 2-*N*-*p*-methoxyphenylamidino-1 : 3-diphenylpropane respectively.

It appeared reasonable to suppose that the aniline salt could with advantage be replaced by a salt of an anthranilic ester in the reaction leading to the formation of 2-amino-4-



(III) (IV)

hydroxyquinoline. However, the products isolated after interaction of ethyl cyanoacetate and the benzenesulphonate of ethyl anthranilate at 140° were 2-ethoxycarbonylmethyl-4-hydroxyquinazolinium benzenesulphonate (III; R = Et, X = Ph·SO_3) and a feebly basic, alkali-soluble compound to which the constitution (IV) is tentatively assigned. With the toluene-*p*-sulphonate of methyl anthranilate, ester exchange occurred, and (III; R = Me, X = *p*-C_6H_4Me·SO_3) was formed; at 210° the products were 4-hydroxy-2-methylquinazolinium benzenesulphonate and the compound (IV). The formation of this 2-methylquinazoline salt is readily accounted for since both the alkoxycarbonylmethylquinazolines (III; R = Et and Me, X = Ph·SO_3 and *p*-C_6H_4Me·SO_3) in boiling acetic acid afforded

4-hydroxy-2-methylquinazoline. The compound (IV) was also obtained together with 4-hydroxy-2-methylquinazoline when (III; R = Me, X = *p*-$C_6H_4Me{\cdot}SO_3$) was heated with methyl anthranilate. Vigorous treatment of (IV) with phosphorus oxychloride yielded a dichloro-compound $C_{17}H_9ON_3Cl_2$ which was soluble in aqueous alkalis.

Experimental

The following *benzenesulphonates* were prepared : 2 : 4-*dimethylanilinium*, needles, m. p. 194—195°, from *iso*propanol (Found : C, 59·9; H, 6·1. $C_{14}H_{17}O_3NS$ requires C, 60·2; H, 6·1%); o-*ethoxycarbonylanilinium*, needles (from *iso*propanol), m. p. 164° (Found : C, 55·8; H, 5·4. $C_{15}H_{17}O_5NS$ requires C, 55·7; H, 5·3%); o-*methoxyanilinium*, needles, m. p. 206°, from ethanol (Found : C, 55·6; H, 5·3. $C_{13}H_{15}O_4NS$ requires C, 55·5; H, 5·4%); 2-*methoxy-5-methylanilinium*, prisms, m. p. 202—203°, from *iso*propanol (Found : C, 57·0; H, 5·5. $C_{14}H_{17}O_4NS$ requires C, 56·9; H, 5·8%); p-*nitroanilinium*, yellow plates (from ethyl acetate), m. p. 239° (decomp.) (Found : N, 9·7. $C_{12}H_{12}O_5N_2S$ requires N, 9·5%).

2-*Amino*-4-*hydroxyquinoline*.—(i) Ethyl cyanoacetate (11·3 g.) and anilinium toluene-*p*-sulphonate (26·5 g., 1 mol.) were heated together at 210° for 75 min. To a solution of the cooled melt in water (40 c.c.) and ethanol (20 c.c.), saturated sodium carbonate solution (50 c.c.) was added and the mixture was shaken thoroughly with chloroform (20 c.c.). The crude product [6·45 g.; m. p. 275—280° (decomp.)] which separated overnight crystallised from aqueous ethanol or water and had m. p. 301—302° (decomp.), undepressed on admixture with an authentic specimen (Gabriel, *Ber.*, **1918**, **51**, 1500); the yield was 5 g. (31%) (Found : N, 17·5. Calc. for $C_9H_8ON_2$: N, 17·5%). The *picrate* separated from ethanol as yellow needles, m. p. 258—259° (decomp.) (Found : N, 18·0. $C_{15}H_{11}O_8N_5$ requires N, 18·0%). 2-*Amino*-4-*hydroxyquinolinium benzenesulphonate* (34%) crystallised when the reaction mixture from ethyl cyanoacetate and anilinium benzenesulphonate was digested with chloroform and occurred as needles, m. p. 248—249°, from water (Found : N, 8·5. $C_{15}H_{14}O_4N_2S$ requires N, 8·8%); its *sulphate* crystallised from water as prisms, m. p. 247—248° [Found : C, 51·4; H, 4·4. $(C_9H_8ON_2)_2H_2SO_4$ requires C, 51·6; H, 4·3%].

The same yield was obtained when the heating was prolonged to 2 hr. or continued for 30 min. at 245°. From experiments in which the period of heating at 210° was 5 to 12 hr. and at 180°, 2 to 5 hr., 20—25% yields of 2-amino-4-hydroxyquinoline were obtained. Change in the quantity of anilinium benzenesulphonate to 0·5 or 2 mols. led to a decrease in the yield to 19%.

The chloroform solution of by-products of the reaction was evaporated to dryness and distilled in steam to remove ethylaniline. Acetanilide was extracted from the residue by means of light petroleum, and the remaining insoluble bases when fractionally crystallised as their picrates from ethanol afforded 2-amino-4-hydroxyquinolinium picrate and *N*-phenylacetamidinium picrate, m. p. and mixed m. p. 191—192° (Found : C, 46·6; H, 3·3; N, 19·1. Calc. for $C_{14}H_{13}O_7N_5$: C, 46·3; H, 3·6; N, 19·3%). Non-basic by-products were isolated by extraction of the basic by-products from a further quantity of the chloroform solution with dilute hydrochloric acid, adsorption of the mixed non-basic materials on a charcoal column, and fractional elution with methanol; in this way malondianilide, m. p. and mixed m. p. 224—225° (Found : C, 71·0; H, 4·9; N, 10·8. Calc. for $C_{15}H_{14}O_2N_2$: C, 70·9; H, 5·5; N, 11·0%), and α-cyanoacetanilide, m. p. and mixed m. p. 198—199° (Found : C, 67·6; H, 4·9; N, 17·5. Calc. for $C_9H_8ON_2$: C, 67·5; H, 5·0; N, 17·5%), were obtained.

(ii) An aqueous-ethanolic solution of the melt obtained when anilinium benzenesulphonate (25·1 g.) and ethyl cyanoacetate (11·3 g., 1 mol.) were heated together at 180° for 30 min. deposited α-cyanoacetanilide (1·3 g., 8%), m. p. and mixed m. p. 199—200°. The mother-liquor, after concentration, afforded on the addition of sodium hydroxide, crude α-*N*-*phenylamidinoacetanilide* (1·9 g., 15%), which had m. p. and mixed m. p. 176·5—177° (decomp.) (see below) after crystallisation from ethanol. Neutralisation of the alkaline mother-liquor furnished 2-amino-4-hydroxyquinoline (0·8 g., 5%), m. p. and mixed m. p. 297—299° (decomp.). In addition aniline (5·9 g., 63%) was recovered.

(iii) α-Cyanoacetanilide (3·2 g.) and anilinium benzenesulphonate (5 g., 1 mol.) were heated together at 210° for 1 hr. On being worked up in the usual manner, 2-amino-4-hydroxyquinoline (0·12 g., 4%), m. p. and mixed m. p. 300—301° (decomp.), was isolated. In addition a water-insoluble, basic fraction was obtained; from this by extraction with lactic acid and basification, there was isolated α-*N*-phenylamidinoacetanilide (0·65 g., 13%), m. p. and mixed m. p. 175—177° (decomp.) after crystallisation from benzene.

Quinisatin Oxime.—2-Amino-4-hydroxyquinoline (5 g.), dissolved in concentrated sulphuric acid (20 c.c.), was treated during 20 min. at 0° with sodium nitrite (5 g.). Next day the viscous mixture was poured on crushed ice (150 g.), and the precipitate was recrystallised from aqueous acetic acid [yield, 5·5 g., 88%; orange prisms, m. p. 209—210° (decomp.)] (Found: C, 56·6; H, 3·3. Calc. for $C_9H_6O_3N_2$: C, 56·8; H, 3·2%). Baeyer and Homolka (*Ber.*, 1883, **16**, 2216) record the m. p. as 208° (decomp.). This compound is an extremely sensitive reagent for ferrous iron; a visible blue colour is obtained at a dilution of 1 in $2·5 \times 10^7$.

2-*Amino*-4-*hydroxy*-6-*methylquinoline.*—The cooled melt obtained by heating *p*-toluidinium benzenesulphonate and ethyl cyanoacetate (1 mol.) together for 1 hr. at 210° furnished, on digestion with chloroform, crude 2-*amino*-4-*hydroxy*-6-*methylquinolinium benzenesulphonate* (39%), m. p. 260—265° (decomp.), which on recrystallisation from water (charcoal) gave needles, m. p. 283—287° (decomp.) (Found: N, 8·8. $C_{16}H_{16}O_4N_2S$ requires N, 8·4%). A solution of this salt in aqueous ethanol afforded, on the addition of ammonia, the *base* which crystallised as needles, m. p. 341—342° (decomp.), from aqueous ethanol (Found: C, 68·8; H, 5·6; N, 16·0. $C_{10}H_{10}ON_2$ requires C, 68·9; H, 5·8; N, 16·1%). Its *picrate* separated as aggregates of yellow needles, m. p. 274—275° (decomp.), from ethanol (Found: N, 17·5. $C_{16}H_{13}O_8N_5$ requires N, 17·4%).

The following quinoline derivatives were prepared in a similar manner from equimolecular quantities of ethyl cyanoacetate and the benzenesulphonate of the appropriate arylamine:

2-*Amino*-4-*hydroxy*-8-*methylquinoline.* *Benzenesulphonate* (34%), prisms, m. p. 295—296° (decomp.), from aqueous *iso*propanol (Found: C, 58·1; H, 4·9; N, 8·4. $C_{16}H_{16}O_4N_2S$ requires C, 57·8; H, 4·9; N, 8·4%); *base*, needles, m. p. 308—311° (decomp.), from aqueous ethanol (Found: loss at 150°/vac., 18·7. Found, on dried material: C, 69·3; H, 5·8; N, 15·8. $C_{10}H_{10}ON_2,2H_2O$ requires H_2O, 17·1. $C_{10}H_{10}ON_2$ requires C, 69·0; H, 5·8; N, 16·1%); *picrate*, yellow rosettes, m. p. 240—241° (decomp.), from aqueous ethanol (Found: N, 17·0. $C_{16}H_{13}O_8N_5$ requires N, 17·4%).

2-*Amino*-4-*hydroxy*-6 : 8-*dimethylquinoline.* *Benzenesulphonate* (39%), needles, m. p. 309—312° (decomp.), from aqueous ethanol (Found: C, 59·3; H, 5·1; N, 7·7. $C_{17}H_{18}O_4N_2S$ requires C, 59·0; H, 5·2; N, 8·1%); *base*, plates, m. p. 317—321° (decomp.) after sintering at 300—311°, from ethanol (Found, on dried material: N, 14·7. $C_{11}H_{12}ON_2$ requires N, 14·9%); *picrate*, yellow needles, m. p. 261—262° (decomp.), from aqueous ethanol (Found: N, 16·7. $C_{17}H_{15}O_8N_5$ requires N, 16·8%).

2-*Amino*-4-*hydroxy*-6-*methoxyquinoline.* *Benzenesulphonate* (29%), plates, m. p. 297—298·5° (decomp.), from aqueous ethanol (Found: C, 55·2; H, 4·6; N, 7·6. $C_{16}H_{16}O_5N_2S$ requires C, 55·2; H, 4·6; N, 8·0%); *base*, prisms, m. p. 293—295° (decomp.), from *n*-butanol–benzene (Found: C, 62·9; H, 4·8; N, 14·6. $C_{10}H_{10}O_2N_2$ requires C, 63·1; H, 5·3; N, 14·7%); *picrate*, yellow needles, m. p. 266—267° (decomp.), from aqueous ethanol (Found: N, 16·3. $C_{16}H_{13}O_9N_5$ requires N, 16·7%).

2-*Amino*-4-*hydroxy*-8-*methoxyquinoline.* *Benzenesulphonate* (28%), needles, m. p. 301—302° (decomp.), from water (Found, on material dried at 150°/vac.: C, 55·1; H, 4·9; N, 7·7. $C_{16}H_{16}O_5N_2S$ requires C, 55·2; H, 4·6; N, 8·0%); *base*, needles (from aqueous ethanol), m. p. 313·5—315° (decomp.) (Found: loss at 150°/vac., 9·1. Found, on dried material: C, 63·0; H, 5·6; N, 15·1. $C_{10}H_{10}O_2N_2,H_2O$ requires H_2O, 8·7. $C_{10}H_{10}O_2N_2$ requires C, 63·1; H, 5·3; N, 14·7%); *picrate*, orange prisms, m. p. 251—251·5° (decomp.), from ethanol (Found: N, 16·4. $C_{16}H_{13}O_9N_5$ requires N, 16·7%).

2-*Amino*-4-*hydroxy*-8-*methoxy*-5-*methylquinoline.* *Benzenesulphonate* (47%), needles, m. p. 312—313° (decomp.), from aqueous ethanol (Found: C, 56·7; H, 4·8; N, 7·8. $C_{17}H_{18}O_5N_2S$ requires C, 56·4; H, 5·0; N, 7·7%); *base*, needles, m. p. 266—268·5° (decomp.), from aqueous ethanol (Found: C, 64·9; H, 6·0; N, 13·5. $C_{11}H_{12}O_2N_2$ requires C, 64·7; H, 5·9; N, 13·7%); *picrate*, yellow needles, m. p. 239—240° (decomp.), from aqueous ethanol (Found: N, 16·0. $C_{17}H_{15}O_9N_5$ requires N, 16·2%).

2-*Amino*-4 : 6-*dihydroxyquinoline.*—Equimolecular quantities of *p*-hydroxyanilinium benzenesulphonate and ethyl cyanoacetate were heated together at 210° for 1 hr. The *base*, isolated in the manner described for 2-amino-4-hydroxyquinoline, crystallised from aqueous ethanol as needles (17%), m. p. 348—349° (decomp.) (Found: loss at 100°/vac., 13·3. Found, on dried material: C, 61·0; H, 4·7; N, 15·7. $C_9H_8O_2N_2,1·5H_2O$ requires H_2O, 13·3. $C_9H_8O_2N_2$ requires C, 61·4; H, 4·6; N, 15·9%). Its *picrate* crystallised as yellow needles, m. p. 280—281° (decomp.), from aqueous ethanol (Found: N, 17·3. $C_{15}H_{11}O_9N_5$ requires N, 17·3%).

The following quinoline derivatives were prepared in a similar manner from the benzenesulphonate of the appropriate arylamine and ethyl cyanoacetate.

2-*Amino*-6-*chloro*-4-*hydroxyquinoline* (21%), needles, m. p. 358—361° (decomp.) from aqueous ethanol (Found: C, 55·4; H, 3·7; N, 14·6. $C_9H_7ON_2Cl$ requires C, 55·5; H, 3·6; N, 14·4%); *picrate*, aggregates of yellow needles, m. p. 282—285° (decomp.), from ethanol (Found: N, 16·6. $C_{15}H_{10}O_8N_5Cl$ requires N, 16·5%).

2-*Amino*-8-*chloro*-4-*hydroxyquinoline* (8%), hygroscopic needles, m. p. 321—323° (decomp.) from aqueous ethanol (Found: loss at 150°/vac., 8·5. Found, on dried material: C, 55·4; H, 3·5; N, 14·2. $C_9H_7ON_2Cl,H_2O$ requires H_2O, 8·5. $C_9H_7ON_2Cl$ requires C, 55·5; H, 3·6; N, 14·4%); *benzenesulphonate*, needles, m. p. 295—296° (decomp.), from water (Found: loss at 150°/vac., 7·3. Found, on dried material: C, 50·9; H, 3·8; N, 8·2. $C_{15}H_{13}O_4N_2ClS,1·5H_2O$ requires H_2O, 7·1. $C_{15}H_{13}O_4N_2ClS$ requires C, 51·0; H, 3·7; N, 7·9%); *picrate*, yellow needles, m. p. 233—235° (decomp.), from aqueous ethanol (Found: N, 16·8. $C_{15}H_{10}O_8N_5Cl$ requires N, 16·5%).

2-*Amino*-3-n-*butyl*-4-*hydroxyquinoline*.—Ethyl 2-cyanohexanoate (8·5 g.) and anilinium toluene-*p*-sulphonate (14 g., 1 mol.) reacted slightly exothermically when heated together at 210° for 2 hr. The crude *toluene*-p-*sulphonate* (10·5 g., 54%), m. p. 220—222°, which separated from a solution of the melt in aqueous ethanol was obtained as prisms, m. p. 227—229°, on recrystallisation from water (Found: C, 61·6; H, 6·7; N, 6·9. $C_{20}H_{24}O_4N_2S$ requires C, 61·8; H, 7·2; N, 6·2%). 2-*Amino*-3-n-*butyl*-4-*hydroxyquinoline* crystallised as elongated prisms, m. p. 237—238° (decomp.), from aqueous ethanol (Found: C, 72·2; H, 7·2; N, 13·2. $C_{13}H_{16}ON_2$ requires C, 72·2; H, 7·4; N, 13·0%).

2-*Amino*-3-n-*butyl*-4-*hydroxy*-6-*methoxyquinoline*.—Equimolecular quantities of *p*-methoxyanilinium benzenesulphonate and ethyl 2-cyanohexanoate were heated together at 210° for 2 hr.; the cooled melt, on digestion with chloroform, afforded crude 2-*amino*-3-n-*butyl*-4-*hydroxy*-6-*methoxyquinolinium benzenesulphonate* (45%), m. p. 205—208°, which on recrystallisation from aqueous ethanol separated as needles, m. p. 218—219° (Found: C, 59·4; H, 5·8; N, 6·8. $C_{20}H_{24}O_5N_2S$ requires C, 59·4; H, 6·0; N, 6·9%). Decomposition of this salt in aqueous-ethanolic solution by the addition of ammonia furnished the *base* which crystallised from ethanol as needles, m. p. 233—235° (decomp.) (Found: C, 68·2; H, 6·9; N, 11·5. $C_{14}H_{18}O_2N_2$ requires C, 68·3; H, 7·4; N, 11·4%). The *picrate* separated as needles, m. p. 229—230·5° (decomp.), from ethanol (Found: N, 15·0. $C_{20}H_{21}O_9N_5$ requires N, 14·7%).

The following quinoline derivatives were prepared in a similar manner from equimolecular quantities of the named arylammonium benzenesulphonate and the named substituted ethyl cyanoacetate:

2-*Amino*-3-*benzyl*-4-*hydroxyquinoline* (53%), from anilinium benzenesulphonate and ethyl α-cyano-β-phenylpropionate; elongated plates, m. p. 298·5—300·5° (decomp.), from aqueous ethanol (Found: C, 76·8; H, 5·1; N, 11·2. $C_{16}H_{14}ON_2$ requires C, 76·8; H, 5·6; N, 11·2%); *benzenesulphonate*, prisms, m. p. 239—240°, from ethanol (Found: C, 64·6; H, 5·0; N, 6·5. $C_{22}H_{20}O_4N_2S$ requires C, 64·7; H, 4·9; N, 6·9%); *picrate*, yellow needles, m. p. 238·5—239° (decomp.), from *iso*propanol (Found: N, 14·4. $C_{22}H_{17}O_8N_5$ requires N, 14·6%).

2-*Amino*-3-*benzyl*-4-*hydroxy*-6-*methoxyquinoline* (47%), from *p*-methoxyanilinium benzenesulphonate and ethyl α-cyano-β-phenylpropionate; needles, m. p. 303—304° (decomp.), from aqueous ethanol (Found: C, 72·8; H, 5·7; N, 10·1. $C_{17}H_{16}O_2N_2$ requires C, 72·8; H, 5·8; N, 10·0%); *benzenesulphonate*, elongated prisms, m. p. 263—264° (decomp.), from aqueous ethanol (Found: C, 62·7; H, 5·0; N, 5·9. $C_{23}H_{22}O_5N_2S$ requires C, 63·0; H, 5·1; N, 6·4%); *picrate*, yellow prisms, m. p. 270—271° (decomp.), from aqueous acetic acid (Found: C, 60·9; H, 4·6; N, 12·2. $C_{23}H_{19}O_9N_5,C_2H_4O_2$ requires C, 60·5; H, 4·1; N, 12·3%).

2-*Amino*-4-*hydroxy*-3-*phenylquinoline* (53%), from anilinium benzenesulphonate and ethyl α-cyanophenylacetate; needles, m. p. 345—349° (decomp.), from aqueous ethanol (Found: C, 76·3; H, 5·3; N, 11·4. $C_{15}H_{12}ON_2$ requires C, 76·3; H, 5·1; N, 11·9%); *benzenesulphonate*, rosettes, m. p. 253—255° (decomp.), from *n*-butanol (Found: N, 7·1. $C_{21}H_{18}O_4N_2S$ requires N, 7·1%); *picrate*, yellow needles, m. p. 221—222·5° (decomp.), from aqueous ethanol (Found: loss at 110°/vac., 3·8. Found, on dried material: C, 54·6; H, 3·6; N, 14·9. $C_{21}H_{15}O_8N_5,H_2O$ requires H_2O, 3·7. $C_{21}H_{15}O_8N_5$ requires C, 54·2; H, 3·3; N, 15·1%).

2-*Amino*-4-*hydroxy*-6-*methoxy*-3-*phenylquinoline* (35%), from *p*-methoxyanilinium benzenesulphonate and ethyl α-cyanophenylacetate; prisms, m. p. 366—368° (decomp.), from aqueous acetic acid (Found: C, 71·8; H, 5·3. $C_{16}H_{14}O_2N_2$ requires C, 72·2; H, 5·3%); *benzenesulphonate*, needles, m. p. 246·5—247°, from *iso*propanol (Found: C, 61·9; H, 5·0; N, 6·4. $C_{22}H_{20}O_5N_2S$ requires C, 62·3; H, 4·8; N, 6·6%); *picrate*, yellow needles, m. p. 228—230° (decomp.), from ethanol (Found: C, 53·5; H, 3·4. $C_{22}H_{17}O_9N_5$ requires C, 53·3; H, 3·5%).

α-*Ethoxycarbonyl*-N-*phenylacetamidine*.—The crude thioimidic ester obtained when a mixture

of ethyl cyanoacetate (11·3 g.) and thioglycollic acid (13·8 g., 1·5 mols.) was saturated with dry hydrogen chloride and kept at 0° for 4 hr. was added to aniline (25 g., 2·7 mols.) in absolute alcohol (100 c.c.). After 3 days, basic material was liberated, collected in benzene, fractionated by extraction with acetate buffer (pH 4·5), liberated to chloroform, and recovered. Fractional crystallisation of the mixed picrates from *iso*propanol afforded *α-ethoxycarbonyl-N-phenylacetamidinium picrate* (0·7 g., 1·6%) as needles, m. p. 146—147° (Found: C, 47·1; H, 3·8; N, 16·2. $C_{17}H_{17}O_9N_5$ requires C, 46·9; H, 3·9; N, 16·1%).

α-N-*Phenylamidinoacetanilide*.—(i) The crude thioimidic ester prepared as in the foregoing experiment was heated with aniline (20 g., 2·1 mols.) on a steam-bath for 4 hr. Basic material was liberated and fractionated by successive fractional partitions between acetate buffer (pH 4·5) and first benzene and then ether. α-N-*Phenylamidinoacetanilide* (1·4 g., 11%) crystallised from methanol as prisms, m. p. 178—179° (decomp.) (Found: C, 71·0; H, 6·1; N, 16·7. $C_{15}H_{15}ON_3$ requires C, 71·1; H, 6·0; N, 16·6%).

(ii) To a mixture of aniline (9·3 g.) and ethyl cyanoacetate (11·3 g., 1 mol.), powdered aluminium chloride (13·4 g., 1 mol.) was gradually added at 130° and the mixture was kept at 130—140° for 30 min. A solution of the product in water furnished, on the addition of sodium hydroxide, α-*N*-phenylamidinoacetanilide (3·2 g., 26%), m. p. and mixed m. p. 178—179° (decomp.). Its *benzenesulphonate* crystallised as flat prisms, m. p. 174°, from ethyl acetate (Found: C, 61·0; H, 5·6; N, 10·4. $C_{21}H_{21}O_4N_3S$ requires C, 61·3; H, 5·2; N, 10·2%). This salt did not afford 2-amino-4-hydroxyquinoline on being heated at 210° for 30 min.

Interaction of ω-Cyanoacetophenone and Anilinium Benzenesulphonate.—ω-Cyanoacetophenone (14·5 g.) and anilinium benzenesulphonate (25·1 g., 1 mol.) were heated together at 210° for 1 hr. From the solid obtained by the addition of sodium hydroxide to an aqueous-ethanolic solution of the melt, basic material was extracted with aqueous lactic acid and reprecipitated. The precipitate furnished from benzene ω-*N*-phenylamidinoacetophenone ((3·3 g., 14%), m. p. 162°, undepressed on admixture with a specimen prepared according to Krishnamurti's method (*J.*, 1928, 415) (Found: N, 11·9. Calc. for $C_{15}H_{14}ON_2$: N, 11·8%) [*picrate*, yellow prisms, m. p. 147—148° (decomp.), from *iso*propanol (Found: N, 15·4. $C_{21}H_{17}O_8N_5$ requires N, 15·0%)]. When shaken with dilute hydrochloric acid, the benzene mother-liquor yielded a resin from which *2-anilino-4-phenylquinoline* (0·45 g., 3%) was recovered and crystallised as pale yellow needles, m. p. 190°, from aqueous ethanol [Found: C, 85·4; H, 5·4; N, 9·4%; *M* (Rast), 294. $C_{21}H_{16}N_2$ requires C, 85·1; H, 5·4; N, 9·5%; *M*, 296]. The *picrate* crystallised from methanol in aggregates of needles, m. p. 240—241·5° (decomp.) (Found: C, 61·6; H, 3·5; N, 13·5. $C_{27}H_{19}O_7N_5$ requires C, 61·7; H, 3·6; N, 13·3%).

1 : 3-*Diphenyl*-2-N-*phenylamidinopropane*.—Ethyl α-benzyl-α-cyano-β-phenylpropionate (7·6 g.) and anilinium benzenesulphonate (9·4 g., 1 mol.) were heated together at 210° for 3 hr. The gum remaining on evaporation of a chloroform extract of the cooled melt was washed thoroughly with ether and basified with ammonia in ethanolic solution. The crude basic material, after purification *via* its lactate, afforded 1 : 3-*diphenyl*-2-N-*phenylamidinopropane* (2 g., 17%) as needles, m. p. 176—177·5°, on crystallisation from *cyclo*hexane (Found: C, 83·9; H, 6·9; N, 8·8. $C_{22}H_{22}N_2$ requires C, 84·0; H, 7·0; N, 8·9%). Its *picrate* crystallised in clusters of needles, m. p. 171—172°, from aqueous acetic acid (Found: N, 13·0. $C_{28}H_{25}O_7N_5$ requires N, 12·9%).

2-N-p-*Methoxyphenylamidino*-1 : 3-*diphenylpropane*.—The melt obtained when ethyl α-benzyl-α-cyano-β-phenylpropionate (7·6 g.) and *p*-methoxyanilinium benzenesulphonate (10·5 g., 1 mol.) were heated together at 210° for 2 hr. was worked up as described for the foregoing compound. 2-N-p-*Methoxyphenylamidino*-1 : 3-*diphenylpropane* (1·1 g., 9%) crystallised as needles, m. p. 135—135·5°, from *cyclo*hexane (Found: C, 80·5; H, 7·0; N, 7·9. $C_{23}H_{24}ON_2$ requires C, 80·2; H, 7·0; N, 8·1%).

Interaction of Ethyl Cyanoacetate and 2-Alkoxycarbonylanilinium Salts.—(i) Ethyl cyanoacetate (5·7 g.) and *o*-ethoxycarbonylanilinium benzenesulphonate (16·2 g., 1 mol.) were heated together at 140° for 2 hr. The material which crystallised from an ethanolic extract of the melt afforded *2-ethoxycarbonylmethyl-4-hydroxyquinazolinium benzenesulphonate* (3·7 g., 19%) as rods, m. p. 205—206° (decomp.), on recrystallisation from ethanol (Found: C, 55·3; H, 4·6; N, 7·2. $C_{18}H_{18}O_6N_2S$ requires C, 55·4; H, 4·7; N, 7·2%). The *base*, liberated by sodium hydrogen carbonate, crystallised from benzene as rods, m. p. 163—164° (decomp.) (Found: C, 62·4; H, 5·1; N, 12·3. $C_{12}H_{12}O_3N_2$ requires C, 62·1; H, 5·2; N, 12·1%). The material insoluble in alcohol furnished 2-(2 : 4-*dihydroxy*-3-*quinolinyl*)-4-*hydroxyquinazoline* (4·7 g., 31%) as needles, m. p. 353—355° (slight decomp.), when crystallised from glacial acetic acid (Found: C, 66·8; H, 3·8; N, 13·9. $C_{17}H_{11}O_3N_3$ requires C, 66·9; H, 3·6; N, 13·8%). Light absorption

in N/50-sodium hydroxide, $\lambda_{max.}$ 221 mμ (ε 53,900), inflection at 230 mμ (ε 47,800), $\lambda_{max.}$ 285 (ε 17,000), $\lambda_{max.}$ 304 (ε 18,000).

(ii) Repetition of the foregoing experiment but with ethyl cyanoacetate and *o*-methoxycarbonylanilinium toluene-*p*-sulphonate afforded *4-hydroxy-2-methoxycarbonylmethylquinazolinium toluene*-p-*sulphonate* (17%) which was crystallised from glacial acetic acid and then from ethanol as prisms, m. p. 221—223° (decomp.) (Found: C, 55·2, 55·4; H, 4·9, 4·7; N, 7·1. $C_{18}H_{18}O_6N_2S$ requires C, 55·4; H, 4·7; N, 7·2%). The corresponding *base* crystallised from benzene as needles, m. p. 184—185° (decomp.) (Found: C, 60·6; H, 4·7; N, 12·9. $C_{11}H_{10}O_3N_2$ requires C, 60·5; H, 4·6; N, 12·8%). The acetic acid mother-liquor slowly deposited 4-hydroxy-2-methylquinazolinium toluene-*p*-sulphonate, m. p. and mixed m. p. 276—277° (decomp.) (see below).

(iii) The benzenesulphonate (32·3 g.) and ethyl cyanoacetate (11·3 g., 1 mol.) were brought into reaction at 210° for 1 hr.; the reaction was strongly exothermic and the melt gradually solidified during the heating. An aqueous extract of the cooled melt deposited on concentration 4-hydroxy-2-methylquinazolinium benzenesulphonate (4·6 g., 14%), m. p. 243—244°; after recrystallisation from aqueous *iso*propanol this had m. p. 245—245·5°, undepressed on admixture with an authentic specimen (see below). The base had m. p. and mixed m. p. 240·5—241° (Found: N, 17·4. Calc. for $C_9H_8ON_2$: N, 17·5%), and its picrate m. p. and mixed m. p. 210—211° (decomp.). The water-insoluble fraction of the melt was extracted with sodium hydroxide and the material precipitated by carbon dioxide furnished on crystallisation from acetic acid 2-(2 : 4-dihydroxy-3-quinolinyl)-4-hydroxyquinazoline, m. p. and mixed m. p. 353—355° (slight decomp.) (6·2 g., 40%).

2-(2 : 4-*Dihydroxy*-3-*quinolinyl*)-4-*hydroxyquinazoline*.—4-Hydroxy-2-methoxycarbonylmethylquinazolinium toluene-*p*-sulphonate (16·2 g.) and methyl anthranilate (6·2 g., 1 mol.) were heated together at 180—200° for 2 hr. 4-Hydroxy-2-methylquinazolinium toluene-*p*-sulphonate was extracted from the product with glacial acetic acid; the insoluble material, after recrystallisation from glacial acetic acid, afforded 2-(2 : 4-dihydroxy-3-quinolinyl)-4-hydroxyquinazoline, m. p. and mixed m. p. 353—355° (slight decomp.) (6·1 g., 50%) (Found: C, 67·0; H, 3·4; N, 13·5. Calc. for $C_{17}H_{11}O_3N_3$: C, 66·9; H, 3·6; N, 13·8). Light absorption in N/50-sodium hydroxide: $\lambda_{max.}$ 220 mμ (ε 53,500), inflection at 230 mμ (ε 47,700), $\lambda_{max.}$ 285 mμ (ε 16,700), $\lambda_{max.}$ 305 mμ (ε 17,500). This compound was soluble in aqueous sodium hydroxide and insoluble in aqueous sodium carbonate and mineral acids.

The foregoing compound (1 g.) was boiled with phosphorus oxychloride (4 c.c.) for 4 hr. and poured into water. Recrystallisation of the solid which separated from aqueous ethanol and from benzene afforded the *dichloro*-derivative as prisms, m. p. 260·5—261·5° (decomp.) (0·62 g., 55%). This compound was readily soluble in cold aqueous sodium hydroxide [Found: C, 59·5; H, 3·0; N, 12·3; Cl, 21·2%; *M* (Rast), 351. $C_{17}H_9ON_3Cl_2$ requires C, 59·7; H, 2·6; N, 12·3; Cl, 20·8%; *M*, 342]. The same compound was obtained when the period of boiling was 14 hr. Unchanged starting material was recovered when an attempt was made to bring about the reaction with a mixture of phosphorus pentachloride and phosphorus oxychloride and when acetylation was attempted under a variety of conditions.

4-Hydroxy-2-methylquinazoline.—(i) A solution of 2-ethoxycarbonylmethyl-4-hydroxyquinazolinium benzenesulphonate (1 g.) in glacial acetic acid was boiled for 1 hr.; the crystals which separated on cooling yielded on treatment with sodium hydrogen carbonate in aqueous solution 4-hydroxy-2-methylquinazoline, m. p. 240—241°, undepressed on admixture with a specimen prepared by Bogert's method (*J. Amer. Chem. Soc.*, 1900, **22**, 129); the *benzenesulphonate* formed needles, m. p. 245—245·5°, from *iso*propanol (Found: N, 9·0. $C_{15}H_{14}O_4N_2S$ requires N, 8·8%), the *toluene*-p-*sulphonate*, prisms, m. p. 276—277° (decomp.), from glacial acetic acid (Found: C, 57·8; H, 5·3. $C_{16}H_{16}O_4N_2S$ requires C, 57·8; H, 4·9%), and the *picrate* yellow needles, m. p. 210—211°, from water (Found: N, 17·9. $C_{15}H_{11}O_8N_5$ requires N, 18·0%).

(ii) 4-Hydroxy-2-methoxycarbonylmethylquinazolinium toluene-*p*-sulphonate (1 g.) was boiled in glacial acetic acid for 30 min.; the crude material which separated on cooling (0·7 g., 82%; m. p. 255—260°) after recrystallisation from glacial acetic acid had m. p. 276—277° (decomp.), undepressed by 4-hydroxy-2-methylquinazolinium toluene-*p*-sulphonate. The identity of these compounds was confirmed by a comparison of samples of the base.

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The Formation of o-*Xylene through* 4 : 5-*Dimethylene*cyclo*hexene.*

By Joan E. Ladbury and E. E. Turner.

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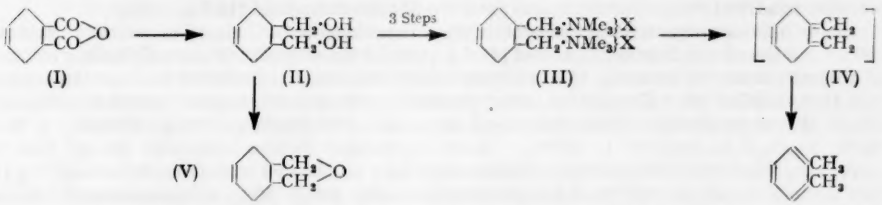
o-Xylene is obtained when 4 : 5-dimethylene*cyclo*hexene is the formal product of the Hofmann degradation of the dimethohydroxide of 4 : 5-di-(dimethylaminomethyl)*cyclo*hexene.

The aim of this investigation was to isolate 4 : 5-dimethylene*cyclo*hexene (IV) and determine the heat of its conversion into *o*-xylene. In fact, the conversion was, from the practical point of view, spontaneous.

Reduction of *cis-cyclo*hexene-4 : 5-dicarboxylic anhydride (I) or of methyl *cis-cyclo*hexene-4 : 5-dicarboxylate with lithium aluminium hydride in ethereal solution gave *cis*-4 : 5-bishydroxymethyl*cyclo*hexene (II). This, following the general procedure of Haggis and Owen (*J.*, 1953, 389), was converted by the action of toluene-*p*-sulphonyl chloride in pyridine solution into the ditoluene-*p*-sulphonate, which with sodium iodide in acetone gave the di-iodide. Combination of this compound with two mols. of trimethyl-



amine gave the quaternary iodide (III; X = I) and, when the dihydroxide (III; X = OH) was heated, *o*-xylene was formed. For identification it was converted into 3 : 4-dimethylbenzenesulphonamide.

An attempt to obtain dimethylene*cyclo*hexene by the Tschugaeff xanthate process was abortive, probably owing to the difficulty of forming the disodium derivative of the diol. 4 : 5-Bishydroxymethyl*cyclo*hexene readily passed into the corresponding cyclic ether, *cis*-2 : 3 : 4 : 5 : 1′ : 4′-hexahydro-3 : 4-benzofuran (V), for example, on distillation, or in presence of dilute sulphuric acid. The cyclic ether was formed during the above-mentioned preparation of the ditoluene-*p*-sulphonate of the diol.

Experimental

Methyl cis-cyclo*Hexene*-4 : 5-*dicarboxylate*.—A mixture of *cis-cyclo*hexene-4 : 5-dicarboxylic anhydride (48 g.), absolute methyl alcohol (500 c.c.), and concentrated sulphuric acid (20 c.c.) was boiled under reflux for 7 hr. Most of the alcohol was distilled off and the remaining liquid was poured into twice its volume of water and then neutralised with solid sodium hydrogen carbonate. The oil which separated was extracted with ether. The ethereal extracts were dried ($MgSO_4$), and the ether was distilled off. The ester (56·5 g., 90%) had b. p. 116—117°/5·5 mm., n_D^{25} 1·4726. This procedure is less complicated than that described by Cope and Herrick (*J. Amer. Chem. Soc.*, 1950, **72**, 983).

cis-4 : 5-*Bishydroxymethyl*cyclo*hexene*.—(*a*) A solution was made of lithium aluminium hydride (7·5 g., 1·2 mols.) in anhydrous ether (500 c.c.). *cis-cyclo*Hexene-4 : 5-dicarboxylic anhydride (25 g., 1 mol.) was added by extraction from a Soxhlet thimble. The mixture was thereafter boiled for an hour. Water and 5% (v/v) sulphuric acid were added until the mixture cleared. The ethereal layer, together with three ethereal extracts of the aqueous layer, was dried (K_2CO_3) and the ether distilled off. The pale-yellow viscous residue was distilled and 10 g. of colourless viscous liquid, b. p. 169—170°/11 mm., n_D^{25} 1·5092, were obtained. A further 4 g. of

product were obtained by exhaustive ether-extraction of the aqueous layer. The total yield of *diol* was 14 g. (60%) (Found : C, 67·6; H, 10·2. $C_8H_{14}O_2$ requires C, 67·6; H, 9·9%).

(*b*) Methyl *cis-cyclo*hexene-4 : 5-dicarboxylate (55 g., 1 mol.) was added dropwise to a mixture of lithium aluminium hydride (13·5 g., 1·3 mols.) in anhydrous ether (400 c.c.). Water and then dilute hydrochloric acid were added and the ethereal layer separated. The aqueous layer was extracted continuously for 24 hr. with ether. The combined ethereal extracts after being dried (K_2CO_3) were evaporated and the residue was distilled. The diol (30 g., 76%) had b. p. 168–170°/11 mm.

Ditoluene-p-*sulphonate of* cis-4 : 5-*Bishydroxymethyl*cyclo*hexene*.—An ice-cold solution of toluene-*p*-sulphonyl chloride (110 g.) in dry pyridine (350 c.c.) was added gradually to a cooled solution of bishydroxymethyl*cyclo*hexene (37·7 g.) in dry pyridine (100 c.c.). Twelve hours later the mixture was poured into an excess of dilute hydrochloric acid. An oil separated and solidified. The whole was extracted with chloroform. The extract was washed with sodium hydrogen carbonate solution, then with water, and finally dried ($MgSO_4$). Removal of the chloroform by distillation gave an oil, which from methanol gave needles (23 g., 19%), m. p. 94·5° (Found : C, 58·7; H, 5·5; S, 14·6. $C_{22}H_{26}O_6S_2$ requires C, 58·6; H, 5·8; S, 14·2%).

cis-4 : 5-*Bisiodomethyl*cyclo*hexene*.—A mixture of the sulphonic *ester* (23 g.) and sodium iodide (33 g.) in dry acetone (360 c.c.) was boiled under reflux for 16 hr. The precipitated sodium toluene-*p*-sulphonate was filtered off (yield 97%) and the acetone was removed in a vacuum. Addition of water gave a heavy oil, which was dissolved in chloroform. The solution was washed with aqueous sodium thiosulphate and then with water. The dried ($MgSO_4$) solution was freed from chloroform and gave the di-iodo-compound (17·5 g., 95%).

cis-4 : 5-*Di*(*dimethylaminomethyl*)cyclo*hexene Dimethiodide*.—A solution in dry acetone (50 c.c.) of the above di-iodo-compound (17·5 g.) was added dropwise to a gently boiling solution of trimethylamine in acetone. The mixture was boiled under reflux for 3 hr., and the acetone was then distilled off. The residue, after treatment with dry ether, gave a solid *dimethiodide*, which after crystallisation from ethanol had m. p. 158—160° (decomp.) (0·8 g.) (Found : I, 52·6; 52·2. $C_{14}H_{30}N_2I_2$ requires I, 52·9%). Some unchanged di-iodo-compound (14 g.) was recovered. When the bisiodomethyl*cyclo*hexene (1·5 g.) was heated with trimethylamine (2 g.) in dry acetone (6 c.c.) at 100° for 2 hr. (sealed glass tube), 0·8 g. (40%) of quaternary iodide was obtained.

Formation of o-*Xylene*.—The quaternary di-iodide (21 g.) was shaken for 2 hr. with moist silver oxide prepared from silver nitrate (40 g.). The mixture was filtered and the residue well washed with water. The washings and the filtrate were combined and distilled. When about 20 c.c. of liquid remained, an oil began to distil. When no more appeared the oil was separated, dried ($MgSO_4$), and distilled from sodium. *o*-Xylene (2 g.), b. p. 143°, n_D^{23} 1·5017, was obtained.

The *o*-xylene was converted into 3 : 4-dimethylbenzenesulphonamide by the method of Huntress and Autenrieth (*J. Amer. Chem. Soc.*, 1941, **63**, 3446) and Huntress and Carten (*ibid.*, 1940, **62**, 511). The sulphonamide crystallised from ethanol in plates, m. p. and mixed m. p. 144—145°.

cis-2 : 3 : 4 : 5 : 1′ : 4′-*Hexahydro*-3 : 4-*benzofuran*.—A mixture of bishydroxymethyl*cyclo*hexene (20 g.) and naphthalene-2-sulphonic acid (3 g.) was distilled. The distillate was saturated with sodium chloride, the layers were separated, and the oil was again heated with the sulphonic acid. Fractionation of the organic material obtained gave 3·8 g. of the *benzofuran*, b. p. 178–179°, n_D^{25} 1·4888 (Found : C, 77·6; H, 9·6. $C_8H_{12}O$ requires C, 77·4; H, 9·7%).

Part of the expense of this investigation was met by a grant from the Hydrocarbon Research Panel of the Institute of Petroleum.

Bedford College, University of London. [*Received, August 3rd*, 1954.]

The Production of Active Solids by Thermal Decomposition. Part IV. Vermiculite.*

By S. J. Gregg and R. K. Packer.

[Reprint Order No. 5340.]

The effect of heat on both natural ("magnesium") (I) and barium-exchanged (II) vermiculite has been examined by subjecting them to a steadily rising temperature on the electrical sorption balance *in vacuo* (I and II) and on a conventional thermal balance "in air" (I only); simultaneous readings of weight loss w, time t, and temperature T were taken, and the quantity $\Delta w/\Delta T$ was plotted against T. The resultant curves (which are somewhat analogous to those of differential thermal analysis) show significant differences between magnesium and barium vermiculite *in vacuo*, and between the vacuum and air experiments for magnesium vermiculite itself.

The thermal "activation" of the natural vermiculite has been studied (i) by heating separate samples for 6 hr. *in vacuo* at a succession of fixed temperatures and measuring the specific surface by sorption of nitrogen and of oxygen, and the apparent density in a number of liquids; and (ii) by heating the same sample at a succession of fixed temperatures T *in vacuo* on a sorption balance, cooling to 25°, and then determining the sorption isotherms of carbon tetrachloride and of water vapour. The specific surface increases fairly steadily over the whole range of temperature and the apparent density varies in a manner which indicates the presence of holes of a molecular size in the products formed at higher temperatures. All the water lost on heating at temperature T can be resorbed on cooling, provided T does not exceed 480° c or so.

The process of exfoliation has been studied with the aid of surface-area measurements; and it has also been shown possible to reduce the specific surface of the exfoliated material by about one-third by squeezing—an example of the adhesion of surfaces at room temperature without the use of high pressures.

On exchange of the Mg^{++} for Ba^{++} ions the vermiculite behaves differently towards water, which is now taken up in two stages.

Vermiculite is a silicate mineral resembling mica both in appearance and in its layer structure (see Grim, "Clay Mineralogy," McGraw-Hill, New York, 1953, p. 72). On gradual heating it loses a considerable amount of water over a wide range of temperature; but if it is "shock-heated" by plunging it into a furnace at, say, 950°, the sudden expulsion of water causes the material to swell greatly, and results in "exfoliated" vermiculite. The quantity of water lost, and the power of exfoliation, can be greatly modified by substituting the exchangeable Mg^{++} ions of the natural substance by various other ions. The specific surface of the exfoliated material as measured by gas sorption (Harris, *J. Amer. Chem. Soc.*, **1949**, **71**, 363) is known to be several times greater than that of the unheated material, and the substance clearly offers an interesting example of a solid rendered "active" by heating; it was accordingly considered worth while to carry out a more detailed investigation of the effect of heat on the substance, somewhat along the lines of earlier studies (cf. Parts II and III, *locc. cit.*).

Materials.—The vermiculite was from South Africa, its exchangeable cation being largely Mg^{++}. The analysis [kindly supplied by Vermiculite (London) Ltd.] was SiO_2, 39·37; TiO_2, 1·25; Al_2O_3, 12·8; Fe_2O_3, 5·45; FeO, 1·17; MgO, 23·37; CaO, 1·46; Na_2O, 0·80; K_2O, 2·46; H_2O, 11·09; CO_2, 0·60; P_2O_5, 0·15; BaO, 0·04; MnO, 0·30; S, 0·14%.

It was in the form of plates *ca.* 1 cm. by 0·5 cm., and before use was ground in a hand-operated coffee mill and sieved, the fraction $-40 + 20$ mesh being used for all experiments. To prepare the "barium" vermiculite, Barshad's procedure was adopted (*Amer. Min.*, 1949, **34**, 675; 1950, **35**, 225; 1948, **33**, 655).

* Parts II and III, *J.*, 1953, 3945, 3951.

Experimental

Both the untreated and the " barium " vermiculite were first submitted to thermogravimetric analysis *in vacuo*, with the aid of an electrical sorption balance (Gregg, *J.*, 1946, 561; Gregg and Sing, *J. Phys. Coll. Chem.*, 1951, **55**, 597). With the pumps running, the temperature of the sample was raised at a uniform rate of 3·5°/min. by means of an external furnace regulated by hand, and readings of weight, time, and temperature (on a resistance thermometer buried in the sample) were taken at frequent intervals. The original vermiculite was similarly analysed " in air " on the open thermal balance (cf. Gregg and Winsor, *Analyst*, 1945, **70**, 336). The results are best represented by plotting $\Delta w/\Delta T$—the average fractional rate of loss of weight per degree, over a short interval of temperature—against temperature T, curves somewhat analogous to those of differential thermal analysis being then obtained.

Next, one and the same batch of the untreated material was heated *in vacuo* on the sorption balance, at each of a succession of fixed temperatures within the range 20—800°, till no further loss in weight occurred. The sorption isotherm of carbon tetrachloride was then measured at 25° to find the specific surface, followed, after outgassing at 25°, by the sorption isotherm of water vapour; the sample remained *in situ* on the balance throughout.

In a further set of experiments *separate* samples of the untreated vermiculite were heated for 6 hr., each at a different fixed temperature, the specific surface of the products being then determined by sorption of nitrogen and of oxygen at −183° (see Gregg and Stephens, *J.*, 1953, 3952, for apparatus). A second set of samples was similarly prepared, and their density determined by immersion in water, in carbon tetrachloride, in decalin (cf. Gregg and Sing, *J. Phys. Coll. Chem.*, 1952, **56**, 388), and sometimes in helium by using the volumetric sorption apparatus mentioned below. At the higher temperatures (above 300° for sorption and above 400° for density) the sample was prepared " in air " on the open thermal balance and then transferred to the container bulb of the apparatus, where it was outgassed for 1 hr. at 20°; but at the lower temperatures the sample was prepared in the bulb by heating it there for 6 hr. under vacuum.

The process of exfoliation was now studied by shock-heating separate samples of the untreated material for 5 min. in a furnace at 650°, 750°, and 950°, severally, and determining the specific surface by means of oxygen sorption. Then, in an attempt to discover how far the accessible surface could be reduced by mechanical pressure the sorption isotherm of carbon tetrachloride at 25° was measured on the 950°-sample both before and after squeezing: by laying the individual pieces (5000 in all) between two boards, and loading the upper one with weights, it was possible to reduce the average thickness 20-fold.

With the barium-exchanged material only two sets of experiments were carried out, *viz.*, thermogravimetric analysis and measurement of the resorption of water on a sample calcined for 4 hr. *in vacuo* at 150°.

Results and Discussion

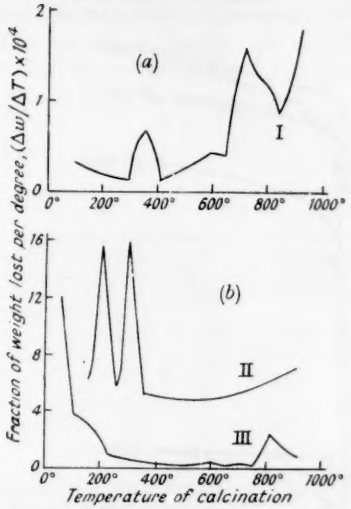
The curve of $\Delta w/\Delta T$ against T, obtained by thermogravimetric analysis of the untreated material, is given in Fig. 1*b*: the peaks at *ca.* 200° and *ca.* 300° " in air " (curve II) agree reasonably with the endothermic peaks, at *ca.* 180° and *ca.* 280°, respectively, obtained in Barshad's differential thermal analysis (*loc. cit.*), and the further slow rise between 600° and 900° shows some correspondence with Barshad's endothermic peak rising from 720° to a maximum at 800°. The curve " *in vacuo* " (curve III) is quite different, showing as it does an almost continuous fall from 50° to 220°. The loss at temperatures below 500°, both in air and *in vacuo*, almost certainly represents molecular rather than structural water, since it is reversible (see later); but at the same time the water cannot *all* be held by van der Waals forces, otherwise it could scarcely require temperatures of 220° in a vacuum or 300° in air for its expulsion; but whether it consists of water of hydration (Hofman and Hausdorf, *Z. Krist.*, 1942, **104**, 265) or merely of specially oriented molecules (cf. Hendricks and Jefferson, *Amer. Min.*, 1938, **23**, 863), or is bound in some other manner, cannot be decided from the present data.

The sorption isotherms of nitrogen and of oxygen are of Type II (B.E.T. classification) so that the specific surface is readily calculated from them (*J. Amer. Chem. Soc.*, 1938, **60**, 309) and is plotted against the temperature of calcination in Fig. 2*b* (curve III and IV).

The sorption isotherms of carbon tetrachloride are likewise of Type II (except for the

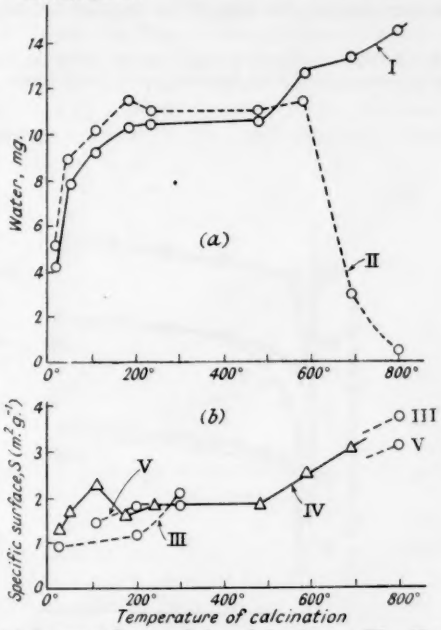
800° sample) but there is no sharp knee, so that, because of the low value of the B.E.T. c, the specific surface cannot be calculated by the ordinary B.E.T. procedure. Instead, it has been assumed (Gregg and Hill, to be published) that the monolayer is complete at or near the point where $p/p_0 = 0{\cdot}5$, and the uptake at this pressure, say $x_{0{\cdot}5}$, has been taken as proportional to specific surface in Fig. 2, curve V. As will be seen, $x_{0{\cdot}5}$ rises sharply from 500° or so upwards, *i.e.*, as the structural water is lost. The finer details of the curve at low temperatures are more doubtful, but combination of the carbon tetrachloride data with those from oxygen and nitrogen sorption leaves little doubt that

FIG. 1. *Thermogravimetric analysis of* (a) *"barium" vermiculite,* (b) *"magnesium" vermiculite.*



I, III, in vacuo; II, *in air. Plot of* $\Delta w/\Delta T$ *against the temperature of calcination* T. (Δw = *fractional change in weight in the temperature interval* ΔT.)

FIG. 2. *Heat treatment of magnesium vermiculite. Various quantities plotted against temperature of calcination* T.



(a) I, *water lost on* 6 *hours' heating at* T°; II, *water resorbed at a relative pressure of* 0·7, *at* 25°.
(b) *Specific surface calculated from sorption isotherms of* III, *nitrogen*; IV, *oxygen*; V, *carbon tetrachloride.*

the specific surface rises fairly steadily from room temperature up to 800°. The lack of data between 300° and 500° is regrettable, but since no loss of water occurs it is probable that the specific surface shows little change over this range.

The results for density (see Table) give information as to pore size (cf., *e.g.*, Franklin, *Trans. Faraday Soc.*, **1949**, **45**, 274). Those measured in helium should be nearest to the

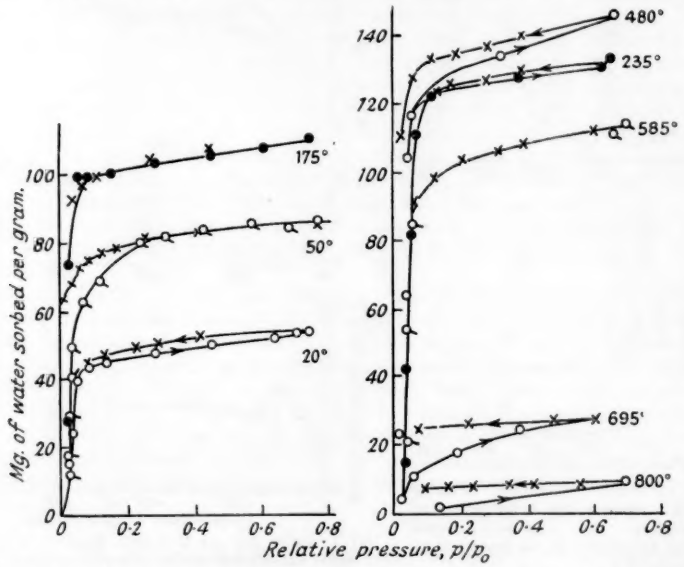
Density (*g. cm.*$^{-3}$) *of vermiculite calcined at various temperatures,* T°, *for* 6 *hours.*

	Density in					Density in			
T°	H_2O	CCl_4	He	$C_{10}H_{18}$ ‡	T°	H_2O	CCl_4	He	$C_{10}H_{18}$ ‡
20 *	2·46	2·33	2·37	—	400 †	2·7	2·56	—	—
50 *	2·5	2·4	—	2·49	500 †	2·80	1·90	—	—
108 *	2·77	2·54	2·56	—	600 †	2·86	1·93	—	1·62
164 *	—	2·62	—	2·22	700 †	2·83	2·37	2·7	1·62
214 *	2·81	2·62	2·58	—	800 †	2·37	2·37	—	1·77
304 *	2·88	2·67	2·71	2·23					

* Prepared in vacuum. † Prepared "in air." ‡ $C_{10}H_{18}$ = Decalin.

true density but high precision is difficult to attain; the density in carbon tetrachloride is approximately the same as in helium for temperatures up to 300°, and falls below it from 400° upwards, whilst the density in decalin lies below both the helium and the carbon tetrachloride value from 164° upwards. Presumably, then, there are (*a*) above 400° holes large enough to admit helium and too small to admit carbon tetrachloride molecules, and (*b*) above 164° further holes large enough to admit carbon tetrachloride (and helium) but too small to admit decalin molecules. From the difference in densities the volume (per g. of solid) of holes of type (*a*) is calculated for the 700° sample to be 0·054 cm.^{3} and of type (*b*) 0·137 cm.^{3}. In water the density increases fairly continuously up to 700° and it is consistently higher than that in any of the other three fluids; this can scarcely be due to a penetration effect, for any holes large enough to admit water molecules should also admit the smaller helium molecules; and it probably signifies an

FIG. 3. *Sorption isotherms of water vapour at 25° on a sample of magnesium vermiculite heated* in vacuo *at a succession of fixed temperatures* T *for 6 hours. The temperature* T *is marked on each isotherm.*



Circles represent adsorption, *crosses* desorption, *measurements. The curve for* 113° *is omitted as it is very close to that for* 175°. *The isotherm for* T = 20° *was measured at* 20°.

increase in the density of the water in the interfacial layer owing to the strong interaction, already referred to, between the water and the solid.

The adsorption isotherms for water vapour (Fig. 3) were of Langmuir type up to the highest pressure studied (usually 0·7p_0); one isotherm, that on the 175° sample, was carried up to saturated vapour pressure and it still remained almost of Langmuir type, though with a slight but significant upward bend between relative pressures of 0·7 and 1·0. Hysteresis was particularly marked with the samples calcined at 695° and 800°; and since the time for equilibration steadily increased from *ca.* 10—15 min. for the 110° sample up to several hours for the 800° sample, the hysteresis is probably due, in part at least, to penetration effects.

In Fig. 2*a* the data for weight lost on calcination due to release of water (w_c, curve I) are compared with those for the weight (w_x, curve II) taken up again at a relative pressure of 0·7, which is situated on the flat portion of the isotherm. As will be seen, the two quantities do not differ greatly for any one temperature of calcination, so long as this is below 480°. Since w_c is calculated from the initial weight of the air-dried sample, which

is somewhat dependent on the relative humidity of the atmosphere, exact agreement between w_c and w_x is not to be expected; and it is fair to infer that the loss of water below 480° or so is completely reversible, whereas at 695°, and still more at 800°, the lattice structure is changed in such a way that most of the lost water cannot be taken up again (cf. Grim, *op. cit.*, p. 74). It should be noted that w_x (or w_c) is far greater than would correspond to a completed monolayer of water molecules adsorbed on the specific surface S: *e.g.*, for the 200° sample this would be only 0·5 mg. or so of water, whereas w_c is *ca.* 103 mg. per g. Thus the resorbed water can reach places inaccessible to nitrogen, no doubt because it can cause the solid to swell (cf. Walker, *Nature*, 1949, **163**, 726).

In one experiment the form of the sorption isotherm in the region near saturation was studied in detail: a 10-g. sample of untreated vermiculite was outgassed at 50° on the sorption balance, to a loss of 8·4% by weight, and the water sorption isotherm measured with the thermostat bath at 15°, *i.e.*, *ca.* 10° below the temperature of the room. Even when the pressure had reached the saturated vapour pressure for 15°, the uptake showed no marked increase, so condensation to bulk liquid had certainly not occurred; nor did it occur when the vapour became supersaturated by allowing the bath to rise to some 3° higher than the temperature of the sample, as measured on the resistance thermometer.

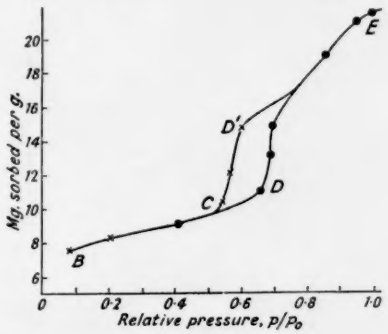


FIG. 4. *Sorption isotherms of water vapour on barium vermiculite at* 15°. *Circles represent* adsorption, *crosses* desorption, *measurements.* (p = *equilibrium pressure*; p_0 = *saturated vapour pressure at* 15°.)

This failure of a supersaturated vapour to condense as bulk liquid on to a porous solid—which implies that there would be a finite contact angle between the adsorbed film and the bulk liquid, corresponding to a difference in entropy between the two states—is of more common occurrence than is usually supposed.

Barium-saturated Vermiculite.—The curve of $\Delta w/\Delta T$ against T for the "barium" vermiculite *in vacuo* (Fig. 1*a*) differs markedly from that for the untreated material both *in vacuo* and in air (Fig. 1*b*). Peaks are now situated at about 360° and 700°, and moreover the *total* loss of water is only 12·7% as compared with 21·3% for the magnesium vermiculite. The shift in, and the lowering of, the high-temperature peak implies that the ion exchange has affected not only the water of "hydration" but the structural water also.

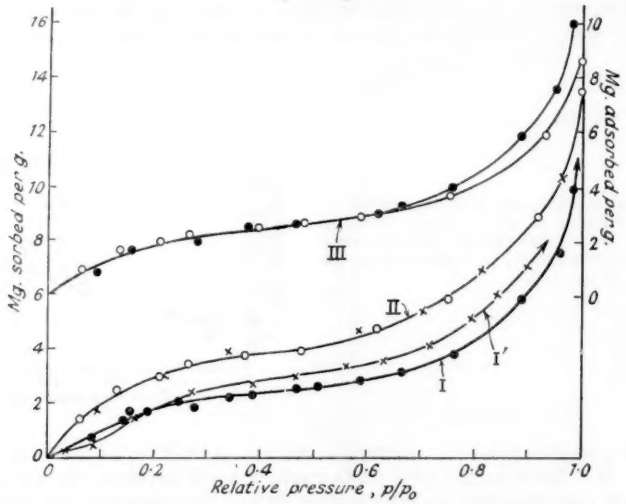
Fig. 4 shows the sorption isotherm of water vapour on a sample of the barium vermiculite which had been heated for 4 hr. *in vacuo* at 150°; *two* distinct steps, *BC* and *CDED'* are now present, the latter comprising a hysteresis loop and, whereas the amount sorbed along *BC* is still fairly close to that lost (*viz.* 7·2%) on the initial calcination *in vacuo*, at *E* it is more than twice this amount.

Comparison with Walker's *X*-ray data (see "X-Ray Identification and Structure of the Clay Minerals," Min. Soc. Monograph, 1951, pp. 199—223) suggests that the two steps correspond respectively to one and two molecular layers of water interleaved between aluminosilicate layers. Walker found for the *c*-spacing of barium-vermiculite 12·3 Å if air-dried, 15·7 Å if wet, and 9·26 Å after heating to 700°; hence the increase in *c*-spacing brought about by the water is 3·04 Å in air-dried and 6·4 Å in the wet material, values close to those expected for one and two molecular layers of water respectively. If

" air-dried " be taken as implying a relative humidity of 40—60%, then the 3·04 Å layer corresponds to the region near *C* of Fig. 4, and the 6·4 Å layer to *E*. The hysteresis loop is probably associated with strains produced in the solid by the swelling (cf. Hirst, *Discuss. Faraday Soc.*, 1948, **3**, 22).

Exfoliation.—The specific surface of the exfoliated product (measured by oxygen sorption) was found to be 2·5, 4·2, and 10·1 m.^{2} g.$^{-1}$ for the temperatures 650°, 750°, and 950° respectively. These areas are far less than the area which would be produced if every aluminosilicate layer were accessible to the oxygen; for, if it is assumed that the thickness of each such layer is 9·26 Å and its density 2·13 g. cm.$^{-3}$, the " theoretical " area would be $2/10^4(2{\cdot}13 \times 9{\cdot}26 \times 10^{-8})$, *i.e.*, 1030 m.^{2} g.$^{-1}$. It thus appears that only a small fraction of the total number of layers is exposed, the average number n of layers per " micelle " of exfoliated solid being 410 at 650°, 240 at 750°, and 100 at 950°. (For

FIG. 5. *Sorption isotherms of carbon tetrachloride vapour on exfoliated vermiculite at* 15°, *before and after squeezing.*



I, I′, *After squeezing*; II, *before squeezing*; III, *superposition of isotherms. The solid circles represent a simple re-plot of* I; *for the open circles the ordinates of* II *have been divided by* 1·6. *Circles represent* adsorption, *crosses* desorption, *measurements. For curves* I *and* II *use left-hand scale, for curve* III *use right-hand scale of ordinates.*

the original vermiculite $n = 1140$ layers, corresponding to a thickness of *ca.* 11 μ per micelle, compared with the average geometrical thickness of the flakes, *viz.*, *ca.* 250 μ. Thus even the original material possesses an appreciable " internal " surface.)

From these data, two possible mechanisms for exfoliation suggest themselves. (*a*) The steam, suddenly liberated between each pair of aluminosilicate layers, forces the layers apart in virtue of its high pressure, so that, for a moment, the full theoretical surface is exposed; but the surface immediately begins to decrease again by sintering (cf. Part I, *J.*, 1953, 3940). (*b*) The steam does not necessarily escape to the exterior along the interplanar channels in which it is liberated, but may find its way into neighbouring channels through cracks *across* the planes until it has accumulated sufficiently in certain channels (actually $1/n$ of the total number of interplanar spaces originally present) to prize apart the bordering layers. Of the two mechanisms (*b*) is the more probable, since according to (*a*) the specific surface should *decrease* with increasing temperature owing to increased sintering, whereas in fact it increases.

It would seem that a minute degree of exfoliation occurs even when the material is heated *gradually* as in the earlier experiments; the original material probably contains

only a single layer of water molecules between the aluminosilicate planes (cf. Walker, *Nature*, 1949, **163**, 726; 1950, **166**, 695), and if this were expelled without disturbance of the main structure, it would leave a channel only 3·3 Å across, whereas the density data show that for temperatures below 300° there are holes large enough to admit carbon tetrachloride molecules, *i.e.*, with a width of at least 5 Å.

Squeezing the exfoliated material reduced the specific surface (as measured by oxygen sorption) from 10·1 to 5·9 $m.^2 g.^{-1}$, *i.e.*, nearly half the surface was either sealed off or destroyed by adhesion of neighbouring micelles.

Now the carbon tetrachloride *adsorption* isotherms at 15° on the squeezed and the unsqueezed samples are found to be superposable within experimental limits (below a relative pressure of *ca.* 0·8) if the ordinates of the " unsqueezed " isotherm are divided by 1·6 (Fig. 5). The sorption over this range must therefore consist solely of adsorption on the walls of the pores and not of capillary condensation; for both the pore sizes themselves and the pore-size distribution would obviously be greatly altered by the squeezing, so that if capillary condensation were present, the ratio of sorption on the two samples would vary with pressure. The presence of a hysteresis loop with the squeezed material does not contradict this conclusion; the loop persists down to a relative pressure of less than 0·2 which, as has been shown, corresponds to a still incomplete monolayer, so that it cannot be ascribed to capillary condensation. More probably the hysteresis is due to a swelling effect which by prizing apart some layers opens up new surfaces (cf. Hirst, *loc. cit.*).

From the carbon tetrachloride isotherms, then, one infers that the squeezing has reduced the specific surface by 1·6-fold, in reasonably good agreement with the 1·7-fold (= 10·1/5·9) reduction inferred from the oxygen isotherms.

The process may be likened to a cold-welding, and is facilitated both by the thinness, and consequent deformability, of the laminæ, and also by their favourable orientation towards one another. These factors explain how it is possible so easily to bring about a reduction in specific surface of an order which usually—as in powder metallurgy—requires high pressure combined with elevated temperature.

Conclusion.—The calcination of magnesium vermiculite represents a somewhat unusual example of the thermal activation of a solid inasmuch as the water is gradually driven off, and the specific surface correspondingly gradually increases, over a wide range of temperature, provided the maximum temperature is approached gradually; and in the fact that the water lost at a temperature as high as 480° is completely taken up again on exposure to water vapour at room temperature.

We thank Dr. R. H. Blathner of Vermiculite (London) Ltd. for kindly supplying the vermiculite together with its analysis; and the Imperial Chemical Industries Research Fund for the loan of apparatus. On of us (R. K. P.) acknowledges receipt of a maintenance grant as student-in-training from the Department of Scientific and Industrial Research.

UNIVERSITY COLLEGE, EXETER. [*Received, April 29th*, 1954.]

The Fries Rearrangement.

By N. M. Cullinane, E. T. Lloyd, and J. K. Tudball.

[Reprint Order No. 5415.]

Titanium tetrachloride has been found to catalyse the rearrangement of phenyl and *o*-tolyl acetates to hydroxyacetophenones. In the latter case, in particular, almost exclusive migration to the *para*-position occurred. The effectiveness of the solvents used was in the order nitrobenzene >*s*-tetrachloroethane >chlorobenzene >benzene. Enhanced yields resulted when more than 1 equivalent of catalyst was employed. Better yields were also obtained when the starting materials were *o*-cresol and acetyl chloride.

Although aluminium chloride is the catalyst usually employed in the conversion of phenol esters into hydroxy-ketones, *e.g.*, $C_6H_5{\cdot}O{\cdot}COR \longrightarrow HO{\cdot}C_6H_4{\cdot}COR$, yet titanium tetrachloride has been found by Ralston, Segebrecht, and McCorkle (*J. Org. Chem.*, 1942, **7**, 522) to catalyse the rearrangement of phenyl hexanoate, and by d'Ans and Zimmer (*Ber.*, 1952, **85**, 585) that of α-naphthyl acetate.

It is generally claimed that the Fries method gives better results than the Friedel–Crafts reaction between phenols and acid chlorides, but it is now shown that under the same experimental conditions the latter can give increased yields of hydroxy-ketones. The Fries method is, however, a convenient one and when carried out with titanic chloride as catalyst in nitrobenzene, *s*-tetrachloroethane, chlorobenzene, or benzene the reaction can be performed in a homogeneous medium, this being more satisfactory than in the absence of a solvent.

The Fries rearrangement.

(0·1 Mole of ester was taken in all cases. The solvent is nitrobenzene, except where otherwise stated.)

$TiCl_4$, mole	Solvent, c.c.	Time (hr.)	Temp.	Yields, % Hydroxy-ketone *p*-	*o*-	*o*-Cresol	$TiCl_4$, mole	Solvent, c.c.	Time (hr.)	Temp.	Yields, % Hydroxy-ketone *p*-	*o*-	*o*-Cresol
						Phenyl acetate							
0·1	50	6	50°	34	6	—	0·1	50	12	50°	42	8	—
0·1	50	9	50	48	9	—							
						o-Tolyl acetate							
0·1	50	6	50	50	3	37	0·3	150	9	30	75	3	14
0·1	50	9	50	58	4	33	0·05	150	9	30	11	trace	19
0·1	50	12	50	56	1	21	0·1	50	9	40	59	2	13
0·05	100	6	30	10	1	25	0·1	50 *	9	40	22	1	26
0·1	100	6	30	47	2	29	0·1	100 *	9	40	20	1	28
0·2	100	6	30	73	2	17	0·1	100 †	9	40	10	trace	21
0·2	100	14	30	78	2	13	0·1	100 ‡	9	40	12	trace	22
0·1	50	9	30	54	1	22	0·1	100	9	40	60	2	20
0·1	100	9	30	50	2	27	0·1	50	20	30	53	2	15
0·1	150	9	30	50	2	24	0·1	50	6	30	47	1	27
0·2	100	9	30	75	2	15	0·1	50	15	30	57	1	16
0·2	150	9	30	75	3	17							
						o-Cresol (0·1 mole) and acetyl chloride (0·1 mole)							
0·1	50	20	30	66	3	15	0·1	100	6	30	48	2	17
0·1	50	6	30	50	3	20	0·1	50	15	30	65	3	16

* *s*-Tetrachloroethane; † benzene; ‡ chlorobenzene.

It is generally held that the solvent may have a pronounced effect on the course of the transformation; the present work shows that nitrobenzene gives much higher yields than tetrachloroethane when used under the same experimental conditions. It is also seen from the Table that variation in the amount of solvent, without change in the other conditions,

has a very slight effect on the reaction. However, variation in the proportion of catalyst to ester up to a molecular ratio of 2 : 1 has a marked effect on yields, although above this ratio the effect is only slight. It should be noted that considerable amounts of the free phenol are always present among the reaction products.

Experimental

Materials.—Precautions were taken to ensure that all the materials used were dry.

Nitrobenzene was dried (P_2O_5) and distilled before use. *s*-Tetrachloroethane was distilled with steam, dried (K_2CO_3), and distilled; the colourless product had b. p. 145·5°. Titanic chloride was boiled under reflux over copper turnings and distilled, yielding a colourless liquid, b. p. 136°. Phenyl and *o*-tolyl acetate, acetyl chloride, and *o*-cresol were distilled before use; the esters gave no colour with ferric chloride solution.

It was found, however, that rigid purification had very little effect on the results obtained.

Action of Titanium Tetrachloride on o-Tolyl Acetate.—In a typical experiment the catalyst was added to a solution of the ester in nitrobenzene immersed in a freezing mixture. The reaction vessel, which was fitted with a mercury seal, was then placed in a thermostat at the required temperature for the requisite time, continuous stirring being maintained throughout. The flask was then cooled rapidly in ice-water, and the dark red homogeneous liquid was treated with dilute hydrochloric acid. Extraction of the nitrobenzene layer with 2*N*-sodium hydroxide gave a solution which contained both 2- and 4-hydroxy-3-methylacetophenones, together with *o*-cresol. After acidification with concentrated hydrochloric acid, distillation with steam removed the *o*-hydroxy-ketone and cresol, the *p*-hydroxy-ketone remaining. This was extracted from the tarry product with boiling water, from which it separated on cooling as prisms, m. p. 104° (Klingel, *Ber.*, 1885, **18**, 2699). Addition of excess of alcoholic 2 : 4-dinitrophenylhydrazine hydrochloride to the steam-distillate precipitated all the *o*-hydroxy-ketone as its dinitrophenylhydrazone, and from the filtrate bromine water precipitated 4 : 6-dibromo-*o*-cresol (OH = 1). The 2 : 4-*dinitrophenylhydrazone* of 2-hydroxy-3-methylacetophenone crystallised from ethyl acetate in red plates, m. p. 252° (decomp.) (Found : N, 17·2. $C_{15}H_{14}O_5N_4$ requires N, 17·0%). The corresponding ***hydrazone*** from 2-hydroxyacetophenone, orange needles from the same solvent, had m. p. 204° (Found : N, 18·0. $C_{14}H_{12}O_5N_4$ requires N, 17·7%).

When *s*-tetrachloroethane was used as solvent, decomposition was brought about by the action of the alkali, trichloroethylene being formed. The tendency to form tar was less marked with tetrachloroethane, chlorobenzene, or benzene than with nitrobenzene. It was also found that, although under the conditions herein described the reaction medium remained homogeneous, the resinous material being formed only on decomposition of the reaction products, yet when larger amounts of catalyst were employed some tar tended to separate during the actual rearrangement.

When ferric chloride (0·2 mole) was substituted for titanic chloride, *o*-tolyl acetate (0·1 mole) in nitrobenzene (50 c.c.), after being heated for 6 hr. at 50°, gave 60% of *p*- and 5% of *o*-hydroxy-ketones. In the absence of any solvent the corresponding yields were 42 and 3%. In the latter experiment the dark mass formed was treated with hydrochloric acid, and the product extracted with ether. Otherwise the separation of products was carried out in the usual way.

When the catalyst used was aluminium chloride (0·1 mole), the ester (0·1 mole) in nitrobenzene (50 c.c.) gave after 24 hr. at 17° a 44% yield of 4- and a 4% yield of 2-hydroxy-3-methylacetophenone.

The usual method was adopted in the reaction between titanic chloride, acetyl chloride, and *o*-cresol, but considerable evolution of hydrogen chloride occurred during the experiment.

We thank Imperial Chemical Industries Limited for a gift of tetrachloroethane. We also thank Peter Spence and Sons Ltd. for a gift of titanium tetrachloride. Two of us (E. T. L. and J. K. T.) are indebted to the University of Wales for Post-graduate Studentships.

The Tatem Laboratories, University College, Cardiff. [*Received, May 26th,* 1954.]

Organometallic and Organometalloidal Fluorine Compounds. Part XI. The Hydrolysis of Trifluoromethylphosphorus Compounds.*

By F. W. Bennett, H. J. Emeléus, and R. N. Haszeldine.

[Reprint Order No. 5455.]

Trifluoromethyl compounds of phosphorus are rarely stable to aqueous or alkaline hydrolysis, and usually yield fluoroform or a mixture of fluoroform and fluoride; examples of the three types are given. Aqueous hydrolysis of $(CF_3)_2PX$ (X = Cl or I) is stepwise, giving first the unstable $(CF_3)_2P{\cdot}OH$ which decomposes to $CF_3{\cdot}P(OH)_2$ and fluoroform. The hydrolysis of $(CF_3)_3P$ is base-initiated; one equivalent of base liberates two equivalents of fluoroform, since the $(CF_3)_2P{\cdot}ONa$ first formed decomposes slowly in the neutral solution to yield sodium trifluoromethylphosphonite and fluoroform. Trifluoromethylphosphonous acid is monobasic, and yields fluoroform in strongly alkaline solution. The reaction of three equivalents of base with di-iodotrifluoromethylphosphine yields sodium trifluoromethylphosphonite quantitatively; addition of a fourth equivalent liberates fluoroform.

The alkaline hydrolysis of tetrakistrifluoromethyldiphosphine is shown to proceed *via* P–P fission. Bistrifluoromethylphosphine decomposes in alkaline solution to give fluoroform, fluoride, and carbonate, and an unidentified trifluoromethylphosphorus acid. The synthesis of mono- and bistrifluoromethylphosphine is described, and their infra-red spectra are presented and discussed. Trifluoromethylphosphonic acid shows extreme stability to hydrolysis.

One of the more interesting properties of certain of the trifluoromethyl compounds of phosphorus described in Parts VII and X (*J.*, 1952, 1565; 1954, 3598) is their ready and quantitative liberation of fluoroform on hydrolysis with aqueous alkali. This behaviour, however, is not shown by all trifluoromethylphosphorus compounds, and the present communication is concerned mainly with the apparently anomalous compounds and with studies on the hydrolysis reactions of phosphorus compounds by water or aqueous alkali.

Three types of behaviour with aqueous alkali can be distinguished: (*a*) hydrolysis yielding fluoroform quantitatively, (*b*) hydrolysis yielding both fluoride and fluoroform, (*c*) marked resistance to hydrolysis.

Compounds which yield only Fluoroform.—Into this class fall the majority of the trifluoromethylphosphorus compounds studied: $(CF_3)_3P$, $(CF_3)_2PX$ (X = I, CN, or Cl), $CF_3{\cdot}PX_2$ (X = I or Cl), $CF_3{\cdot}P(OH)_2$.

The hydrolysis of the compounds of type $CF_3{\cdot}PX_2$ by water alone proceeds as expected: halide ion is liberated, trifluoromethylphosphonous acid, $CF_3{\cdot}P(OH)_2$, is formed, and the solution becomes homogeneous. The hydrolysis of iodobistrifluoromethylphosphine by water occurs in two stages: the reactants are initially immiscible, but as the iodo-compound (the lower layer) disappears evolution of fluoroform occurs from the upper aqueous layer, *i.e.*,

$$(CF_3)_2PI + H_2O \longrightarrow (CF_3)_2P{\cdot}OH + HI$$

$$(CF_3)_2P{\cdot}OH + H_2O \longrightarrow CF_3{\cdot}P(OH)_2 + CHF_3$$

Chlorobistrifluoromethylphosphine similarly yields trifluoromethylphosphonous acid and one equivalent of fluoroform when hydrolysed by water. The phosphonous acid is monobasic and stable to water, but liberates fluoroform quantitatively in alkaline solution.

The stepwise liberation of fluoroform from the compounds $(CF_3)_2PX$ led to a closer investigation of the hydrolysis of tristrifluoromethylphosphine, which liberates fluoroform quantitatively when treated with an excess of aqueous base. Tri-alkyl- and -aryl-phosphines are stable to hydrolysis under most conditions, and the fluoro-compound resembles

* Part X, *J.*, 1954, 3598. Part IX (*J.*, 1954, 881) was incorrectly called Part VIII.

more closely the esters of phosphorous acid in this respect. Thus triphenyl phosphite is hydrolysed by water to phenol and phosphorous acid, 2-chloroethyl diphenyl phosphite yields 2-chloroethanol and phenol, and diethyl and dipropyl phosphites undergo stepwise hydrolysis with water or very dilute alkali (Noack, *Annalen*, 1883, **218**, 85; Kabachnik, *Bull. Acad. Sci. U.R.S.S.*, 1947, 631; *Chem. Abs.*, 1948, **42**, 5845; Milobendzki and Sachnowski, *Chem. Polski*, 1917, **15**, 48; *J.*, 1918, **114**, I, 478; Nylen, *Svensk Kem. Tidskr.*, 1937, **49**, 29, 79). Tristrichloromethylphosphine has recently been reported to hydrolyse to chloroform and phosphite (Yakubovich and Ginsburg, *Doklady Akad. Nauk U.S.S.R.*, 1952, **82**, 273; *Chem. Abs.*, 1953, **47**, 2685), and there is some evidence that phosphorus trichloride undergoes stepwise hydrolysis (Mitchell, *J.*, 1925, **127**, 336; Voigt, *Compt. rend.*, 1951, **232**, 2442). In general, the attachment of negative groups to phosphorus favours rapid hydrolysis.

The hydrolysis of tristrifluoromethylphosphine is base-initiated since, although the compound is stable to water at 100°, addition to a mixture of tristrifluoromethylphosphine and water at 20° of sufficient alkali to liberate theoretically one equivalent of fluoroform actually liberates two equivalents. The reaction occurs in two stages. The first,

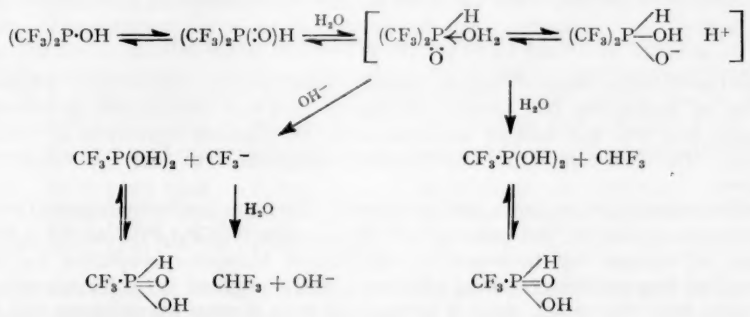
$$(CF_3)_3P + OH^- \longrightarrow (CF_3)_2P{\cdot}O^- + CHF_3$$

is rapid, and is followed by the slow liberation of fluoroform from the now neutral solution :

$$(CF_3)_2P{\cdot}O^- + H_2O \longrightarrow CF_3{\cdot}P(OH){\cdot}O^- + CHF_3$$

The final solution is still neutral with weak reducing properties, and on evaporation to dryness yields sodium trifluoromethylphosphonite (see Part X, *loc. cit.*). The hydrolysis of phosphorus oxyfluoride by water also proceeds stepwise, and in dilute alkaline solution the reaction practically ceases after conversion into the acid HPO_2F_2 (Lange, *Ber.*, 1929, **62**, 786).

The decomposition of bistrifluoromethylphosphinous acid in aqueous or alkaline solution presumably involves the initial co-ordination of a water molecule or attack by a hydroxide ion, followed by rearrangement and decomposition :



The decomposition of bistrifluoromethylphosphinous acid is acid-catalysed, since, when it is prepared in presence of hydriodic acid by the aqueous hydrolysis of iodobistrifluoromethylphosphine, liberation of the equivalent of fluoroform is much more rapid than from the neutral solution obtained from tristrifluoromethylphosphine as described above. The hydrolysis of di*iso*propyl phosphorofluoridate similarly shows acid and base catalysis (Kilpatrick and Kilpatrick, *J. Phys. Chem.*, 1949, **53**, 1388).

Trifluoromethylphosphonous acid is also formed by the aqueous hydrolysis of diiodotrifluoromethylphosphine. Three equivalents of aqueous sodium hydroxide can be added to the last compound without liberation of fluoroform, *i.e.*,

$$CF_3{\cdot}PI_2 + 3NaOH \longrightarrow 2NaI + CF_3{\cdot}P(OH)(ONa) \rightleftharpoons CF_3{\cdot}PH(:O)(ONa)$$

and the infra-red spectrum of the solid obtained on evaporation of the aqueous solution is the same as that of the solid obtained from tristrifluoromethylphosphine and 1 equiv. of aqueous sodium hydroxide. Addition of a fourth equivalent of aqueous base liberates fluoroform quantitatively, just as the reaction of tristrifluoromethylphosphine with two equivalents of aqueous base liberates almost the theoretical amount of fluoroform:

$$CF_3{\cdot}PH(:O){\cdot}O^- + OH^- \longrightarrow CHF_3 + HPO_3^{2-}$$

Fluoroform is also liberated from trifluoromethylphosphonous acid merely by heating its aqueous solution at 100°: $CF_3{\cdot}P(OH)_2 \xrightarrow{H_2O} CHF_3 + H_3PO_3$.

The evaporation by freeze-drying of concentrated solutions of trifluoromethylphosphonous acid prepared by the aqueous hydrolysis of di-iodotrifluoromethylphosphine causes the acid to undergo reaction to give a solid dibasic phosphorus acid and trifluoromethylphosphine (see p. 3903). This reaction does not occur when more dilute solutions are evaporated, and the volatile trifluoromethylphosphonous and hydriodic acids evaporate, leaving no residue.

Compounds which liberate both Fluoride and Fluoroform.—The first trifluoromethyl derivative of a metalloid which was observed to yield both fluoride and fluoroform on hydrolysis by aqueous base was tetrakistrifluoromethyldiphosphine (Part VII, *loc. cit.*). This unusual reaction has been studied further, and its course is now clear. Alkaline hydrolysis (10% sodium hydroxide) yields 75% of the total trifluoromethyl content as fluoroform, *i.e.*, one mole of the diphosphine yields three moles of fluoroform. The solution from the alkaline hydrolysis contains fluoride ion representing 9% of the original trifluoromethyl content; neutralisation of this solution and evaporation to dryness yields a solid whose infra-red spectrum shows strong bands at 8·85 (broad), 9·2 (sharp side band), and 10·2 μ (sharp) revealing the presence of a trifluoromethyl group. The covalent fluorine content of the solid trifluoromethyl compound (probably disodium trifluoromethylphosphonate) accounts for a further 13% of the fluorine in the tetrakistrifluoromethyldiphosphine. The weight balance for fluorine is thus CHF_3 75%, F^- 9%, CF_3–P compound 13%.

The mechanism suggested for this hydrolysis of tetrakistrifluoromethyldiphosphine involves hydrolytic fission of the P–P bond:

$$(CF_3)_2P{\cdot}P(CF_3)_2 \xrightarrow{H_2O} (CF_3)_2PH + (CF_3)_2P{\cdot}OH$$

and since the decomposition of bistrifluoromethylphosphinous acid in basic solution gives two mols. of fluoroform (see above), it follows that the unidentified trifluoromethylphosphorus acid and the fluoride ion must arise by alkaline hydrolysis of bistrifluorophosphine. The last compound was therefore synthesised to test the validity of the mechanism.

Bistrifluoromethylphosphine is best prepared by the reduction by hydrogen of iodobistrifluoromethylphosphine in the presence of Raney nickel [$(CF_3)_2PI \longrightarrow (CF_3)_2PH$]; replacement of halogen by hydrogen in substituted halogeno-phosphines by catalytic hydrogenation has not been reported hitherto. The phosphine (b. p. 1°) appears to form a compound with the nickel, since it is removed from it only by pumping and heating. Reaction of tetrakistrifluoromethyldiphosphine with hydrogen and Raney nickel also gives bistrifluoromethylphosphine, but in smaller yield. Attempts to prepare the phosphine by lithium aluminium hydride reduction of iodobistrifluoromethylphosphine (cf. the successful preparation of bis- and mono-trifluoromethylarsine, Part VI, *J.*, 1953, 1551), or by a photochemical reaction between the iodo-compound and hydrogen [$(CF_3)_2PI \longrightarrow (CF_3)_2P{\cdot} \xrightarrow{H_2} (CF_3)_2PH$] were unsuccessful.

Trifluoromethylphosphine was prepared in low yield by the lithium aluminium hydride reduction of di-iodotrifluoromethylphosphine, but the use of Raney nickel and hydrogen failed to yield the phosphine. This failure may be attributed to compound formation with the nickel, since there was no evidence of unchanged di-iodo-compound, or of etching of the glass reaction vessel, and volatile products were not obtained on strong heating.

An alternative explanation is the formation of polymeric material by reaction of the trifluoromethylphosphine formed initially with unchanged di-iodo-compound:

$$CF_3{\cdot}PH_2 + CF_3{\cdot}PI_2 \longrightarrow CF_3{\cdot}P{:}P{\cdot}CF_3 + 2HI$$

$$n\text{-}CF_3{\cdot}PH_2 + n\text{-}CF_3{\cdot}PI_2 \longrightarrow H{\cdot}\underset{CF_3}{P}\!\!-\!\!\underset{CF_3}{P}\!\!-\!\!\underset{CF_3}{P}\cdots\underset{CF_3}{PI} + 2HI$$

Reaction of di-iodotrifluoromethylphosphine with anhydrous hydrazine or with zinc and hydrochloric acid (cf. preparation of trifluoromethylarsine, Part VI, *loc. cit.*) also failed to yield trifluoromethylphosphine. The most convenient method for the preparation of the last compound is, however, by hydrolysis of di-iodotrifluoromethylphosphine in highly concentrated aqueous solution, followed by freeze-drying of the solution; trifluoromethylphosphine (b. p. −26·5°) is liberated during the last process:

$$CF_3{\cdot}PI_2 \longrightarrow CF_3{\cdot}P(OH)_2 \longrightarrow CF_3{\cdot}PH_2$$

Bistrifluoromethylphosphine and trifluoromethylphosphine are spontaneously inflammable. Unlike dimethylphosphine, bistrifluoromethylphosphine forms no solid addition compounds with methyl iodide, carbon disulphide, silver iodide, or chloroplatinic acid. When heated with iodine the trifluoromethyl compound reacts quantitatively to give an equimolar mixture of trifluoroiodomethane and fluoroform.

The infra-red spectra of the trifluoromethylphosphines show strong absorption bands at 8—9 μ ascribed to C–F stretching vibrations. Since phosphorus is much heavier than hydrogen, it is to be expected that the movement in a P–H bond is largely that of the hydrogen atom, *i.e.*, the P–H stretching vibration should be fairly constant and substantially independent of the other groups attached to the phosphorus atom. In accord with this, the P–H stretching vibrations in trifluoromethylphosphine (C.S. No. 134) and bistrifluoromethylphosphine (C.S. No. 133) appear as strong bands at 4·31 and 4·30 μ, readily distinguished from the weaker C–F overtone bands which also appear in the 4·2—4·3 μ region. The infra-red spectrum of phosphine shows a triplet centred on 4·32 μ (4·17, 4·32, 4·44 μ) which is in good agreement with the P–H vibration assigned at 4·29 μ from the Raman spectrum (Daasch and Smith, *Analyt. Chem.*, 1951, **23**, 853). The P–H bending vibration in phosphine is at 8·92, 10·09 μ, but since this vibration is much more sensitive to the nature of the other substituents on the phosphorus atom, there is a marked shift in the trifluoromethylphosphines; the triplet at 11·90, 12·04, 12·17 μ in trifluoromethylphosphine, and the 12·35 or possibly the 11·70 μ band in bistrifluoromethylphosphine are ascribed to this vibration. A band appears at 13·3—13·6 μ in the spectra of all the trifluoromethyl compounds so far studied, as is shown in the annexed Table, and by analogy with other trifluoromethyl compounds is assigned to a trifluoromethyl deformation

$(CF_3)_2PH$	13·27, 13·35, 13·43	$CF_3{\cdot}PH_2$	13·34, 13·47, 13·65	$CF_3{\cdot}PO(ONa)_2$	13·6
$(CF_3)_2PI$	13·34, 13·40	$CF_3{\cdot}PI_2$	13·55	$CF_3{\cdot}PO(OH)(ONa)$	13·5
$(CF_3)_2PCl$	13·25, 13·32	$CF_3{\cdot}PCl_2$	13·30, 13·34	$(CF_3)_4P_2$	13·37
$(CF_3)_2P{\cdot}CN$	13·24, 13·34	$CF_3{\cdot}P(OH)(ONa)$	13·6	$(CF_3)_3P$	13·25, 13·73

frequency, although the P–$C_{aliph.}$ stretching vibration has been noted in this region for compounds which do not contain fluorine.

When hydrolysed with aqueous alkali under precisely the same conditions as used for tetrakistrifluoromethyldiphosphine, bistrifluoromethylphosphine yields 50% of its trifluoromethyl content as fluoroform, and 18% is present in the residual solution as fluoride and carbonate. Evaporation of the hydrolysate to dryness gives a solid whose infra-red spectrum is identical with that of the solid obtained from the diphosphine, and the covalent fluorine content of the solid is equivalent to 28% of the fluorine content of the bistrifluoromethylphosphine. Thus by the postulated mechanism for the hydrolysis of tetrakistrifluoromethyldiphosphine, 1 mole of the diphosphine would be expected to give 2 moles of fluoroform from $(CF_3)_2P{\cdot}OH$, and 1 mole of fluoroform from $(CF_3)_2PH$, a total of 3 moles, as is actually found. The fluoride ion and the trifluoromethyl phosphorus acid formed during the hydrolysis of the diphosphine would be expected to be equivalent to 9% and

14% respectively of the fluorine content of the diphosphine, and the favourable agreement of these figures with the experimental values of 9 and 13% (see above) is strong support for the postulated mechanism.

The theory is strengthened by the isolation of bistrifluoromethylphosphine when tetrakistrifluoromethyldiphosphine is hydrolysed by water or dilute hydrochloric acid at 100°; fluoroform (2 mols.) is also produced. Trifluoromethylphosphonous acid, which is formed from bistrifluoromethylphosphinous acid at room temperature by loss of fluoroform, reacts with water at 100° to give fluoroform quantitatively; bistrifluoromethylphosphine, however, is only partly decomposed, to give trifluoromethylphosphine (1 mol.), fluoride, and carbon dioxide, and no fluoroform:

$$(CF_3)_2P{\cdot}P(CF_3)_2 \xrightarrow{H_2O} (CF_3)_2PH + (CF_3)_2P{\cdot}OH$$

$$\downarrow H_2O \qquad\qquad \downarrow H_2O$$

$$CF_3{\cdot}PH_2 + F^-, CO_3^{--} \qquad CHF_3 + CF_3{\cdot}P(OH)_2 \xrightarrow[100°]{H_2O} CHF_3$$

This accounts for the liberation of 3 mols. of fluoroform when tetrakistrifluoromethyldiphosphine is treated with aqueous alkali, and of only 2 mols. when heated with water.

The bonding of hydrogen to elements such as arsenic, phosphorus, nitrogen, oxygen, or sulphur which also carry a trifluoromethyl group thus reduces the stability of the normally extremely stable trifluoromethyl group to such an extent that the group readily decomposes into fluoride and carbonate.

Trifluoromethylphosphine also decomposes readily by aqueous alkali, to give 65—70% of the theoretical amount of fluoride ion.

Compounds which do not liberate Fluoride or Fluoroform.—Only one trifluoromethylphosphorus compound has so far shown marked resistance to hydrolysis, *viz.*, trifluoromethylphosphonic acid. This compound, which can be prepared by oxidative hydrolysis of the compounds $(CF_3)_2PX$ or $CF_3{\cdot}PX_2$ (X = I or Cl) (see Part X), has now been obtained quantitatively by an alternative route involving oxidation of trifluoromethylphosphine with 30% nitric acid. Trifluoromethylphosphonic acid is extremely stable, and fails to react with concentrated sulphuric acid at 140° or with 10% sodium hydroxide at 100°; a very slow hydrolysis occurs in alkaline solution at 150°. In this respect trifluoromethylphosphonic acid resembles more the alkyl- and aryl-phosphorus compounds, where the breaking of the P–C bond during hydrolysis is rare.

It should perhaps be emphasised finally that the C–Z bond in a compound CF_3–Z is usually very resistant to hydrolytic attack {*e.g.*, CF_3I, $CF_3{\cdot}CO_2H$, $(CF_3)_3N$, $CF_3{\cdot}SF_5$, $CF_3{\cdot}[CF_2]_n{\cdot}CF_3$, $(CF_3)_2S$}, and in only relatively few cases does the C–Z bond break with liberation of the CF_3 group as fluoroform [$CF_3{\cdot}CO{\cdot}CF_3$, $CF_3{\cdot}CHO$, $CF_3{\cdot}COPh$, $(CF_3)_3As$, $(CF_3)_2AsX$ (X = I, CN, Cl, SCN, Br, or F), $CF_3{\cdot}AsX_2$ (X = I, Cl, or Br), $(CF_3)_3AsX_2$ (X = F or Cl), $(CF_3)_2AsO{\cdot}OH$], or decomposition of the CF_3 group to fluoride and carbonate [$CF_3{\cdot}OF$, $(CF_3)_4As_2$, $(CF_3)_2NH$, $(CF_3)_2O_2$, $CF_3{\cdot}SH$, $(CF_3)_2AsH$].

Experimental

The general techniques used have been described earlier in this series. Reactions were carried out in sealed Pyrex tubes or in conventional ground-glass apparatus. Oxygen was carefully excluded at all times. The products were identified tensimetrically and by molecular-weight determination, and identity was confirmed by examination of infra-red spectra. The reactants and products were manipulated in a vacuum system where practicable, since handling losses are then negligible. For preparation of starting materials see Part VII (*loc. cit.*).

Bistrifluoromethylphosphine.—(a) *From iodobistrifluoromethylphosphine.* (i) With Raney nickel and hydrogen. Pressures of hydrogen of less than 1 atm. have been used, in tubes or flasks of 50—1000 ml. capacity. The Raney nickel catalyst (2 g.; prepared in the usual way) as a slurry in ethanol was poured into the vessel, which was then evacuated to remove the ethanol (30 hr.). A known weight of iodobistrifluoromethylphosphine was then added and

the vessel was filled with almost 1 atm. of hydrogen and sealed. After being heated at 100° (4—20 hr.) the vessel was cooled by liquid nitrogen and opened, and the excess of hydrogen removed by pumping. Pumping was continued whilst the flask was heated at 150° (1 hr.). The combined volatile products were then fractionated *in vacuo*. In one experiment the final heating was effected by use of a naked flame instead of an oil-bath, but this brought about a vigorous exothermic reaction with incandescence, and the yield dropped appreciably.

In a typical reaction, iodobistrifluoromethylphosphine (0·562 g.) in a 50 ml. tube with 600 mm. pressure of hydrogen at 110° (16 hr.) gave *bistrifluoromethylphosphine* (65%), b. p. 1° (isoteniscope) (Found: 66·1%; *M*, 170. C_2HF_6P requires F, 67·0%; *M*, 170).

Catalytic reduction of the iodo-compound can be detected at room temperature, but is inconveniently slow. At 100°, some hydrogen fluoride is liberated, since there is appreciable etching of the apparatus; small amounts of phosphine and fluoroform are also formed.

(ii) With lithium aluminium hydride. In a single experiment, iodobistrifluoromethylphosphine (0·896 g.) in sodium-dried dibutyl ether (10 ml.) was added dropwise to lithium aluminium hydride (0·080 g.) in dibutyl ether (10 ml.). The mixture was heated at 70° (6 hr.) with stirring, but after the cautious addition of water, fractionation of the volatile products *in vacuo* failed to yield bistrifluoromethylphosphine.

(iii) By photochemical reaction with hydrogen. Since iodobistrifluoromethylphosphine readily liberates iodine on irradiation, its photochemical reaction with hydrogen was investigated; iodobistrifluoromethylphosphine (0·729 g.) was sealed in a 100-ml. Pyrex tube with dry hydrogen at 47 cm. pressure. Iodine crystals had appeared after 16 hours' irradiation, but slowly disappeared when the light was turned off. The products obtained after 3 months' irradiation were iodobistrifluoromethylphosphine (0·612 g., 84%), a small quantity of di-iodotrifluoromethylphosphine, and only a trace (0·005 g.) of more volatile material.

(b) *From tetrakistrifluoromethylphosphine.* The diphosphine (0·484 g.) was sealed with hydrogen (650 mm. pressure) in a 500-ml. bulb which was then heated at 65—75° (10 hr.). Fractionation of the products *in vacuo* gave bistrifluoromethylphosphine (0·135 g., 28%) (Found: *M*, 167), identified by means of its vapour pressure and its infra-red spectrum.

A single attempt to convert tetrakistrifluoromethyldiphosphine into bistrifluoromethylphosphine by reaction with zinc and hydrochloric acid was unsuccessful.

The formation of bistrifluoromethylphosphine during the aqueous hydrolysis of the diphosphine is considered below.

Properties of Bistrifluoromethylphosphine.—The compound is unchanged after 3 days at 210—215°. Its constitution follows from an experiment in which bistrifluoromethylphosphine (0·1221 g.) and an excess of dry iodine were heated at 280° (2 days) to give fluoroform (0·0518 g., 51%) and trifluoroiodomethane (0·139 g., 49·5%), identified tensimetrically and by their molecular weights and spectra.

Bistrifluoromethylphosphine does not form a solid addition compound when mixed at room temperature with methyl iodide, carbon disulphide, silver iodide, or chloroplatinic acid.

Trifluoromethylphosphine.—(a) *From di-iodotrifluoromethylphosphine.* (i) By use of lithium aluminium hydride. A solution of di-iodotrifluoromethylphosphine (2·02 g.) in butyl ether (15 ml.) was added dropwise to lithium aluminium hydride (0·19 g.) in butyl ether (10 ml.). There was no reaction in the cold, but at 70° effervescence occurred; after reaction at this temperature for 6 hr. water was added and the volatile products were removed by pumping. Fractionation of these products gave *trifluoromethylphosphine* (0·035 g., 6%), b. p. (isoteniscope) −25·5° (Found: F, 55·6%; *M*, 102. CH_2F_3P requires F, 55·9%; *M*, 102), and a mixture (0·11 g.) of phosphine and trifluoromethylphosphine which could not be separated by distillation.

A similar reaction with lithium aluminium hydride (0·34 g.) in ethyl ether (20 ml.) and di-iodotrifluoromethylphosphine (1·54 g.) in ethyl ether (10 ml.) was more vigorous, and no heating was necessary. The volatile products present after the addition of water were fractionated to give trifluoromethylphosphine (0·035 g., 8%) (Found: *M*, 102), identified by means of its infra-red spectrum.

Lithium aluminium hydride reacted violently with di-iodotrifluoromethylphosphine in absence of a solvent, to give a bright yellow solid, but trifluoromethylphosphine was not formed. The colour indicates a stable complex, since fluoroform was not a reaction product.

(ii) By use of hydrogen and Raney nickel. In an experiment typical of several unsuccessful attempts to prepare trifluoromethylphosphine in an analogous manner to that used for bistrifluoromethylphosphine, di-iodotrifluoromethylphosphine (1·90 g.), Raney nickel (3 g.), and hydrogen (at 600 mm. in a 500-ml. flask) were heated at 65° for 30 min. Distillation of the

volatile condensable products gave small unidentified fractions, but no trifluoromethylphosphine. Strong heating *in vacuo* of the residual Raney nickel gave an unidentified non-inflammable liquid, but no trifluoromethylphosphine.

(iii) By hydrolysis. This forms the most convenient synthesis of the phosphine. See p. 3903.

Oxidation of Trifluoromethylphosphine.—The phosphine (0·143 g.) was sealed *in vacuo* with 4·1N-nitric acid (2 ml.) and shaken (12 hr.). Concentrated nitric acid (2 ml.) was then added, and the resealed tube was again shaken (12 hr.). Evaporation of the solution to dryness by freeze-drying (2 days) and vacuum sublimation of the residue gave trifluoromethylphosphonic acid (0·21 g., 96%; 0·17 g., 82% when resublimed). The disodium salt of the acid had an infra-red spectrum identical with that of the salt prepared from the acid made by alternative routes (Part X, *loc. cit.*).

Hydrolysis Reactions.—(a) *Tristrifluoromethylphosphine.* (i) With an excess of alkali. Tristrifluoromethylphosphine (0·392 g.), sealed *in vacuo* with sodium hydroxide (1 g.) and water (15 ml.), underwent immediate reaction, and after 48 hr. yielded fluoroform (0·338 g., 98%).

(ii) With 1 equiv. of alkali. Tristrifluoromethylphosphine (0·655 g., 2·75 mmoles) was sealed in a tube with sodium hydroxide (24 ml. of 0·1146N; 2·75 mmoles) and shaken vigorously at room temperature (1 hr.). Fractionation gave unchanged tristrifluoromethylphosphine (0·055 g., 8%) and fluoroform [0·177 g., 33% based on $P(CF_3)_3$ comsumed]. One trifluoromethyl group has thus been lost from the missing tristrifluoromethylphosphine, and the aqueous solution contains $(CF_3)_2P{\cdot}ONa$ at this stage.

The reaction tube was resealed and shaken for a further 2 days. A further quantity of fluoroform (0·173 g., 33%) had then been produced. Thus the initial rapid loss of one trifluoromethyl group as fluoroform is followed by a slower loss of a second group as fluoroform. The residual aqueous solution contained sodium trifluoromethylphosphonite, since on treatment with an excess of aqueous sodium hydroxide the final equivalent of fluoroform (0·173 g., 33%) was evolved.

In a further experiment tristrifluoromethylphosphine (0·226 g., 0·95 mmole) and aqueous sodium hydroxide (8·26 ml. of 0·1146N; 0·95 mmole) were shaken at 20° for 84 hr. to give unchanged tristrifluoromethylphosphine (0·022 g., 9%) and fluoroform (0·123 g., 68%). The residual solution was evaporated to dryness and the infra-red spectrum of the residual white solid (0·125 g.) showed it to be sodium trifluoromethylphosphonite.

(b) *Iodobistrifluoromethylphosphine.* (i) With water. Iodobistrifluoromethylphosphine (0·484 g.), shaken with water (2 ml.) for 7 hr. at 20°, gave fluoroform (0·114 g., 48%). The iodo-compound initially formed a lower layer with the water, and as the lower layer disappeared gas was evolved from the aqueous layer. Evaporation of the residual aqueous solution at 20°/10^{-2} mm. left no residue. The aqueous condensate liberated fluoroform quantitatively when treated with an excess of aqueous alkali.

(ii) With acid. Iodobistrifluoromethylphosphine (0·537 g.) underwent an immediate effervescence with N-hydrochloric acid (15 ml.), and after 5 days at 20° had yielded fluoroform (0·120 g., 47%).

(iii) With alkali. The iodo-compound (0·188 g.), shaken with an excess of 10% sodium hydroxide solution (15 ml.) for 24 hr., gave fluoroform (0·088 g., 99%).

(c) *Di-iodotrifluoromethylphosphine.* (i) With alkali. Reaction of an excess of aqueous sodium hydroxide (10 ml.; 10%) with di-iodotrifluoromethylphosphine (0·385 g.) yielded fluoroform (0·076 g., 100%).

(ii) Stepwise hydrolysis by alkali. The aqueous hydrolysis of di-iodotrifluoromethylphosphine yields an acid solution which can be treated with up to three successive equivalents of aqueous alkali before evolution of fluoroform occurs. This was shown as follows: Di-iodotrifluoromethylphosphine (0·718 g., 2·03 mmoles) was placed in an evacuated, 500-ml., two-necked flask, one neck of which was sealed with a rubber cap through which could be pushed a hypodermic needle; the second neck was connected to a trap cooled in liquid oxygen to collect volatile products. Water (2 ml.) was added and the flask was set aside until hydrolysis of the iodo-compound was complete, as indicated by the disappearance of the yellow lower layer. One equivalent of 0·496N-sodium hydroxide (4·15 ml., 2·05 mmoles) was then added *via* the hypodermic needle; no fluoroform was evolved. A second equivalent of sodium hydroxide was then added, and again there was no evolution of fluoroform. Addition of a third equivalent of sodium hydroxide, diluted by water (5 ml.), caused slight evolution of fluoroform (0·018 g., 12%). A 15-ml. portion of the solution was then evaporated to dryness to give a white solid (0·511 g.), shown to contain sodium trifluoromethylphosphonite by means of its infra-red spectrum.

In a further experiment di-iodotrifluoromethylphosphine (0·708 g., 2 mmoles) was hydrolysed by water (1 ml.). 0·29 Equiv. more than the theoretical 3 equiv. of sodium hydroxide was then added (13·24 ml. of 0·496N-sodium hydroxide, 6·58 mmoles). Fluoroform in an amount corresponding to the excess of base added was liberated (0·042 g., 0·6 mmole, 30%). Addition of a large excess of aqueous alkali at this stage liberated the rest of the trifluoromethyl groups as fluoroform. The stepwise hydrolysis thus shows that aqueous hydrolysis of the di-iodo-compound yields trifluoromethylphosphonous acid and 2 mols. of hydrogen iodide.

(iii) With limited amounts of water to produce trifluoromethylphosphine. Di-iodotrifluoromethylphosphine (5·34 g., 0·0151 mole) and water (1—2 ml.) were allowed to react at 20° until hydrolysis was complete (3 hr.) as indicated by the merging of two layers. The solution was then evaporated to dryness by freeze-drying (14 days) and the evolved water and gases were condensed in a trap cooled by liquid oxygen. The residue from the freeze-drying procedure was a white solid (1·42 g.), initially believed to be a new acid of empirical formula $CF_3{\cdot}P(OH)_2,H_2O$ (see Part VII), but subsequently shown (Paul, unpublished observations) to be trifluoromethylphosphonic acid. The condensate collected in the liquid-oxygen trap consisted of water, hydrogen iodide, and trifluoromethylphosphine (0·363 g., 24%) (Found: *M*, 103), identified by means of its infra-red spectrum.

(d) *Chlorobistrifluoromethylphosphine.* (i) With water. The compound (0·467 g.), shaken with water (2 ml.), underwent immediate reaction, and after 3 hr. the volatile product was examined and shown to be fluoroform (0·157 g., 49%).

(ii) With alkali. The chloro-compound (0·160 g.) reacted vigorously with an excess of aqueous sodium hydroxide (10 ml. of 10%) to give fluoroform (0·109 g., 67%) after 3 days.

(e) *Dichlorotrifluoromethylphosphine.* (i) With water. The chloro-compound (0·233 g.) underwent a vigorous reaction with water (1 ml.) at room temperature and the two layers soon became homogeneous. When evaporated to dryness at $20°/10^{-2}$ mm., the aqueous solution left no residue; treatment of the condensate (collected in a trap cooled by liquid oxygen) with an excess of 10% aqueous sodium hydroxide yielded fluoroform (0·092 g., 90%).

In a second experiment dichlorotrifluoromethylphosphine (0·233 g.) was sealed with water (2 ml.), then allowed to warm to room temperature. There was an immediate exothermic reaction, but gas was not evolved. The mixture was frozen, an excess of aqueous sodium hydroxide (6 ml. of 10%) was added, and the tube resealed. There was an immediate evolution of gas at room temperature, and fractionation, etc., showed this gas to be fluoroform (0·092 g., 96%). These experiments show that dichlorotrifluoromethylphosphine is hydrolysed to trifluoromethylphosphonous acid which is volatile in water vapour and unstable to base.

(ii) With alkali. Reaction of dichlorotrifluoromethylphosphine (0·215 g.) with an excess of aqueous sodium hydroxide (10 ml. of 5%) at 20° gave fluoroform (0·088 g., 99%).

(f) *Cyanobistrifluoromethylphosphine.* Hydrolysis of this compound (0·105 g.) with an excess of aqueous sodium hydroxide (10 ml. of 10%) at 20° (4 days) yielded fluoroform (0·074 g., 99%).

(g) *Bistrifluoromethylphosphine.* (i) By water. There is no reaction with water at room temperature. The phosphine (0·184 g.) and water (5 ml.), heated *in vacuo* at 110—130° (50 hr.), gave carbon dioxide, unchanged bistrifluoromethylphosphine (26%), and trifluoromethylphosphine (0·065 g., 39%). The volatile products were identified by their infra-red spectra. The aqueous solutions contained fluoride (36%).

(ii) By aqueous alkali. Bistrifluoromethylphosphine (0·2266 g.) and aqueous sodium hydroxide (0·5 g. in 10 ml. of water) liberated a gas at room temperature. After 2 weeks, fractionation of the volatile products gave fluoroform (0·0948 g., 51%) (Found: *M*, 70). The aqueous solution contained fluoride (0·027 g., 17·8%) as shown by distillation as fluorosilicic acid and titration with thorium nitrate.

The experiment was repeated with bistrifluoromethylphosphine (0·1968 g.), sodium hydroxide (0·75 g.), and water (10 ml.). The products were fluoroform (0·0813 g., 50%), fluoride (0·0233 g., 17·7%, by titration), and a trifluoromethylphosphorus acid. The last compound was detected by neutralisation of an aliquot of the solution followed by freeze-drying. The infra-red spectrum of the residual solid revealed the presence of a trifluoromethyl group; the solid was fused with sodium at 550—600° (4 hr.), and the total fluoride obtained was equivalent to 46% of the bistrifluoromethylphosphine. The covalent fluorine in the solid (*i.e.*, as trifluoromethylphosphorus acid) was thus 28·3%, and the weight balance for fluorine is 96%.

(h) *Trifluoromethylphosphine.* In a single experiment, trifluoromethylphosphine (0·106 g.) was sealed with aqueous sodium hydroxide (0·5 g. in 5 ml. of water), and the reaction tube was set aside for 7 days. Fluoride (72%) was formed, and after neutralisation of the solution,

evaporation to dryness gave a white solid whose infra-red spectrum suggested the presence of an unidentified compound containing covalent fluorine.

(i) *Attempted hydrolysis of trifluoromethylphosphonic acid.* The acid (0·204 g.), sealed in a Carius tube with 10% sodium hydroxide (15 ml.), and heated at 150° (10 hr.), yielded no fluoroform; fluoride (0·009 g., 12·5%) had been liberated and was estimated by the thorium nitrate method.

Trifluoromethylphosphonic acid (0·036 g.) was mixed with concentrated sulphuric acid (50 ml. of 50%) and heated to 135—140°. Steam was then passed through the mixture, and the condensed distillate was analysed for fluoride; none was detected. Since only a small amount (0·05 ml.) of 0·5N-sodium hydroxide was required to neutralise the distillate, it follows that trifluoromethylphosphonic acid is not volatile in steam.

(j) *Reactions of trifluoromethylphosphonous acid.* (i) When heated in acid solution. A solution of this acid, prepared by the reaction of iodobistrifluoromethylphosphine (0·537 g.) with an excess of N-hydrochloric acid at room temperature, was heated to 100° for 16 hr. to give fluoroform (0·125 g., 49%). In a second experiment, a solution of the acid, prepared by the reaction of iodobistrifluoromethylphosphine (0·182 g.) with water, was heated at 100° for 12 hr. to give fluoroform (0·043 g., 50%).

(ii) With aqueous alkali. When a solution of trifluoromethylphosphonous acid, prepared by the reaction of di-iodotrifluoromethylphosphine (0·71 g., 0·002 mole) with an excess of water, was treated with an excess of aqueous sodium hydroxide, a quantitative evolution of fluoroform was found.

(iii) With two equivalents of alkali. Tristrifluoromethylphosphine (0·172 g., 0·72 mmole), shaken with aqueous sodium hydroxide (12·57 ml. of 0·1146N; 1·44 mmoles) for 84 hr., gave fluoroform (0·137 g., 91%) and not more than a trace of unchanged tristrifluoromethylphosphine.

(k) *Hydrolysis of tetrakistrifluoromethyldiphosphine.* This compound was prepared as described earlier (*J.*, 1953, 1565).

(i) By water. The diphosphine (0·209 g., 0·62 mmole) failed to react with water (10 ml.) during 36 hr. at 20°. Fluoroform (0·089 g., 1·3 mmoles, 51%) (Found: *M*, 70) and bistrifluoromethylphosphine (0·064 g., 0·4 mmole, 32%), b. p. 1° (Found: *M*, 170. Calc. for C_2HF_6P: *M*, 170), were formed by reaction at 100° for 24 hr., and were identified spectroscopically.

(ii) By acid. The diphosphine (0·566 g., 1·7 mmoles) and 1·25N-hydrochloric acid (25 ml.) failed to react at 20°, and after 24 hr. at 100° two layers were still present. The liquid phase became homogeneous after a further 12 hr. at 100°. Fractionation of the volatile products gave fluoroform (0·224 g., 48%) (Found: *M*, 70) and bistrifluoromethylphosphine (0·232 g., 41%) (Found: *M*, 169).

(iii) By alkali. Tetrakistrifluoromethyldiphosphine (0·508 g.), sealed *in vacuo* with 10% aqueous sodium hydroxide (10 ml.), underwent vigorous reaction (5 min.) with evolution of gas. The reaction tube was set aside (10 days) with intermittent shaking, and fractionation of the volatile products then gave fluoroform (0·310 g., 75%) (Found: *M*, 70). Determination of the fluoride in one-fifth of the solution showed that fluoride (0·031 g., 9%) had been produced. A neutralised portion (60% of original) of the residual liquid was evaporated to dryness by freeze-drying to give a white solid (1·220 g.). The infra-red spectrum of the solid showed it to contain C–F bonds. A portion of the solid (0·823 g.) was fused with sodium at 600° (3 hr.) and the ionic fluoride was then determined to be 0·0762 g., *i.e.*, 22%. Since 9% was present as ionic fluorine before sodium fusion, 13% must have been present as covalent fluorine in the unknown trifluoromethylphosphorus acid. Alkaline hydrolysis of tetrakistrifluoromethyldiphosphine thus yields fluoroform (75%), fluoride (9%), and a trifluoromethylphosphorus acid (13%).

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Xanthones and Thioxanthones. Part V. The Preparation and Properties of 9-Thia-2-aza-anthrone and 9-Thia-4-aza-anthrone.*

By S. KRUGER and FREDERICK G. MANN.

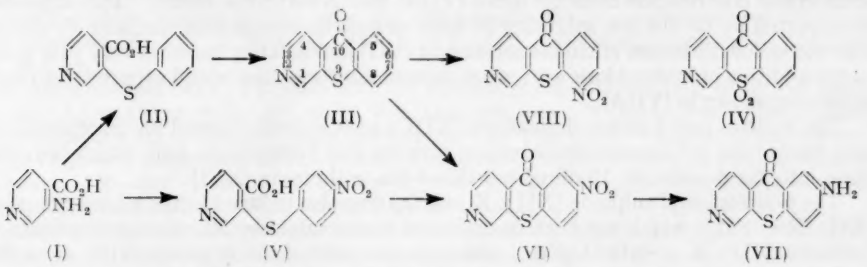
[Reprint Order No. 5471.]

The synthesis of the two compounds named in the title and of various derivatives and kindred compounds is described. Certain of these compounds have been tested as possible schistosomicides but found to be ineffective.

IN Part IV,* Mann and Reid described the synthesis of 9-oxa- and 9-thia-1-aza-anthrone: these compounds and certain derivatives were prepared in order to investigate their possible value as schistosomicides.

We have now synthesised 9-thia-2-aza-anthrone (III) and 9-thia-4-aza-anthrone (XI): our synthetic route in each case was unfortunately not applicable to the 9-oxa-analogues which still await preparation.

To prepare the 2-aza-anthrone (III), diazotised 3-amino*iso*nicotinic acid (I) was condensed with thiophenol in alkaline solution to form 4-carboxy-3-pyridyl phenyl sulphide (II). This was converted by thionyl chloride into the carbonyl chloride which when heated in nitrobenzene with aluminium chloride readily cyclised to give 9-thia-2-aza-anthrone (III). In this series, as in the 1-aza-series, the quaternary methochloride and the sulphone were chosen for therapeutic investigation. The anthrone (III) underwent ready quaternisation when heated with methyl toluene-*p*-sulphonate, and the product furnished in turn the methiodide and methochloride. Hydrogen peroxide in acetic acid oxidised (III) at 75—80° to the 9 : 9-dioxide (IV), the identification of which as the sulphone, in contradistinction to the sulphoxide amine oxide, was confirmed by its infra-red spectrum



Diazotised 3-amino*iso*nicotinic acid (I) and *p*-nitrothiophenol in alkaline solution similarly formed the *p*-nitrophenyl sulphide (V), and thence, as before, pale yellow 6-nitro-9-thia-2-aza-anthrone (VI), which on reduction with tin (or stannous chloride) and hydrochloric acid gave the bright red crystalline 6-amino-derivative (VII).

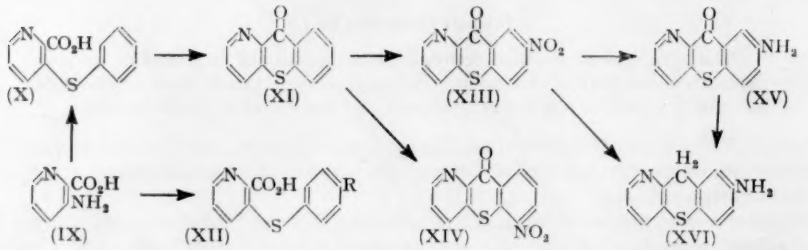
The parent anthrone (III) when cautiously nitrated gave a product which was apparently a mixture of the 6- and the 8-nitro-derivative (VI and VIII), but these components could not be satisfactorily isolated by fractional crystallisation or sublimation. Reduction, followed by fractional sublimation, gave however the red 6-amino-derivative (VII), m. p. 227°, and a more volatile yellow crystalline product, m. p. 183°, which was presumably the 8-amino-derivative, although insufficient material precluded identification. The colour of the amine (VII) is discussed later.

In the 4-aza-series, 3-aminopicolinic acid (IX) was similarly converted into 2-carboxy-3-pyridyl phenyl sulphide (X), which, when treated as (II), furnished the 9-thia-4-aza-anthrone (XI). This compound was also converted into the methiodide, methochloride, and sulphone.

The acid (IX) was also converted into 2-carboxy-3-pyridyl *p*-nitrophenyl sulphide (XII; R = NO_2), but attempts, under a wide variety of conditions, to cyclise this compound

* Part IV, *J.*, 1952, 2057.

failed. This was unfortunate, because no mono-nitro-derivative of the anthrone (XI) of certain orientation was therefore available for reference purposes. Nitration of the anthrone (XI) gave two mononitro-derivatives: the one which formed considerably the major

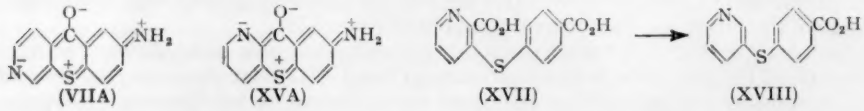


product separated as pale yellow crystals, m. p. 298°, and the other as bright yellow crystals, m. p. 249°. The former is almost certainly the 6-nitro-derivative (XIII) and the second is the 8-nitro-derivative (XIV), as nitration would occur more readily in the position *para* to the sulphur atom than in that *ortho* to this atom. This assumption (which for brevity of reference will be accepted) receives some confirmation from reduction of the former nitro-derivative to a scarlet amino-compound, presumably (XV)—in the 2-aza-series the derivative with the amino-group *para* to the sulphur has also this strikingly intense colour. The second nitro-compound (XIV) gave a brownish-yellow amino-compound, too small in quantity for further investigation.

It is suggested that the bright red colour of the 6-aminoanthrones (VII) and (XV) is due to charge separation, with the result that the resonance hybrids of these amines receive a considerable contribution from the forms (VIIA) and (XVA) respectively. This suggestion is supported by (*a*) the low solubility of these amines in organic solvents, and (*b*) the fact that the yellowish-brown ethanolic solution of (VII) immediately becomes very pale yellow on the addition of hydrochloric acid, when normal salt formation would suppress the charge separation shown in (VIIA).

The 6-nitro- and 6-amino-derivatives (XIII and XV) both showed an unexpected and very ready type of Clemmensen reduction with tin and hydrochloric acid, which converted them into the 6-amino-9 : 10-dihydro-9-thia-4-aza-anthracene (XVI).

The *p*-nitrophenyl sulphide (XII; R = NO_2) was also reduced to the amino-compound (XII; R = NH_2), which was both de-aminated to the sulphide (X) and converted into the urethane (XII; R = ·NH·CO_2Et). Although the yield of the sulphide (XII; R = NO_2) is markedly greater than that of the sulphide (X) from the acid (IX), this alternative route to (X) *via* the amine (XII; R = NH_2) offers no advantage.



The diazotised acid (IX) also underwent condensation with methyl *p*-mercaptobenzoate to give ultimately *p*-carboxyphenyl 2-carboxy-3-pyridyl sulphide (XVII), which, like (XII, R = NO_2), could not be cyclised to the corresponding thia-anthrone: it underwent ready monodecarboxylation however to *p*-carboxyphenyl-3-pyridyl sulphide (XVIII), the structure of which was proved by its non-identity with the isomeric acid (X).

In Part IV it was noted that tests kindly undertaken by Mr. O. D. Standen at the Wellcome Laboratories of Tropical Medicine had shown that 9-thia-1-aza-anthrone and its sulphone had no significant effect on schistosomiasis infections. Subsequent tests by Mr. Standen have given the same result for the methochloride of this anthrone, for the acid (X), and also for the 2-aza- and 4-aza-anthrones (III and XI) and for their sulphones and methochlorides.

Experimental

4-Carboxy-3-pyridyl Phenyl Sulphide (II).—A solution of 3-amino*iso*nicotinic acid (I) (6·3 g.) (Gabriel and Colman, *Ber.*, 1902, **35**, 2832) in concentrated hydrochloric acid (10 c.c.) was stirred at 5° whilst a solution of sodium nitrite (3·6 g., 1·13 mols.) in water (25 c.c.) was added dropwise. Ten minutes after complete addition, urea was added to destroy excess of nitrous acid, and the solution was then added slowly with stirring to one of sodium hydroxide (10 g.) and thiophenol (5 c.c., 1 mol.) in water (50 c.c.) at 95°, heating being maintained until evolution of nitrogen ceased. The filtered chilled solution was then brought to pH 5 by the addition of acetic acid, whereupon the cream-coloured *sulphide* (II) was precipitated, m. p. 227° (decomp.) after crystallisation from acetic acid (yield, 4·7 g., 44%) (Found: C, 62·3; H, 3·9; N, 6·3. $C_{12}H_9O_2NS$ requires C, 62·3; H, 3·9; N, 6·1%).

9-Thia-2-aza-anthrone (III).—A mixture of the sulphide (II) (3 g.) and thionyl chloride (15 c.c.) was boiled under reflux for 1 hr., and the excess of chloride then removed in a vacuum. Nitrobenzene (30 c.c.) and aluminium chloride (8 g.) were added to the residue, and the mixture was then heated at 100° for 3 hr., poured on ice, and steam-distilled to remove the nitrobenzene. The hot solution was filtered, cooled, and strongly basified with sodium hydroxide. The precipitated solid was collected, washed, dried, and sublimed at 160—170°/0·2 mm., furnishing the *anthrone* (III) (2 g., 72%) as cream-coloured needles, m. p. 165° (Found: C, 67·6; H, 3·3; N, 6·6. $C_{12}H_7ONS$ requires C, 67·6; H, 3·3; N, 6·6%). It gives a reddish-yellow solution in concentrated sulphuric acid.

The anthrone (1·1 g.) and methyl toluene-*p*-sulphonate (22 g.) were heated at 165° for 4 hr., and when cold repeatedly extracted with ether; the oily residue, when dissolved in water and treated with concentrated aqueous sodium iodide, deposited the *methiodide*, orange needles, m. p. 250—251° (decomp.) after recrystallisation from water (Found: C, 43·8; H, 2·9; N, 3·8. $C_{13}H_{10}ONIS$ requires C, 43·9; H, 2·8; N, 3·9%). A suspension of an excess of freshly prepared silver chloride in a solution of the methiodide (1·5 g.) in methanol (100 c.c.) was boiled under reflux for 20 min. in the absence of light, then filtered, and the solvent was removed; the residue, recrystallised from methanol–ether, gave the yellow *methochloride monohydrate* (0·6 g.), m. p. 244° (decomp.) (Found: C, 55·7; H, 4·6; N, 5·0. $C_{13}H_{10}ONClS,H_2O$ requires C, 55·4; H, 4·6; N, 5·0%).

9-Thia-2-aza-anthrone 9 : 9-Dioxide (IV).—A solution of the anthrone (III) (0·9 g.) in acetic acid (90 c.c.) was kept at 75—80° whilst 30% hydrogen peroxide (6 c.c.) was added in three portions during 4 hr., the heating being then continued for 2 hr. more. On cooling, the *sulphone* (IV) (0·72 g., 69%) separated, and crystallised from ethanol as cream-coloured needles, melting indefinitely 230—250° (decomp.) (Found: C, 58·8; H, 2·7; N, 5·6. $C_{12}H_7O_3NS$ requires C, 58·8; H, 2·8; N, 5·7%). For infra-red data see below.

4-Carboxy-3-pyridyl p-Nitrophenyl Sulphide (V).—This *sulphide* was prepared in 93% yield precisely as (II) but with *p*-nitrothiophenol, and when recrystallised from acetic acid formed pale yellow needles, m. p. 279° (decomp.) (Found: C, 52·5; H, 3·2; N, 10·0. $C_{12}H_8O_4N_2S$ requires C, 52·2; H, 2·9; N, 10·1%).

6-Nitro-9-thia-2-aza-anthrone (VI).—This *compound* was prepared as (III), but with 6 hours' heating of the final mixture, and when sublimed at 200°/0·05 mm. furnished pale yellow needles, m. p. 290° (Found: C, 56·0; H, 2·45; N, 11·0. $C_{12}H_6O_3N_2S$ requires C, 55·8; H, 2·3; N, 10·8%).

6-Amino-9-thia-2-aza-anthrone (VII).—Stannous chloride (1 g.) was added to a suspension of the nitro-anthrone (VI) (50 mg.) in concentrated hydrochloric acid (5 c.c.), which was kept at 60° for 1 hr., and then cooled and made strongly alkaline with sodium hydroxide. When the precipitated material was heated at 205°/0·03 mm., the *amino*-compound (VII) (20 mg.) sublimed to form bright red crystals, m. p. 227° (Found: C, 63·3; H, 3·5; N, 12·1. $C_{12}H_8ON_2S$ requires C, 63·2; H, 3·5; N, 12·3%). The same compound was obtained when the stannous chloride was replaced by tin.

Nitration of the Anthrone (III).—Finely powdered potassium nitrate (75 mg.) was added to a stirred solution of the anthrone (100 mg.) in cold concentrated sulphuric acid (20 c.c.), the colour of the solution changing from reddish-yellow to pure yellow. The solution was poured on ice and made alkaline with ammonia. The yellow precipitate (100 mg.), when collected, washed with water, dried, and sublimed at 200—210°/0·2 mm., melted indefinitely between 230° and 280° and consisted of mixed mononitro-derivatives (Found: C, 55·9; H, 2·5; N, 10·7. $C_{12}H_6O_3N_2S$ requires C, 55·8; H, 2·3; N, 10·8%).

The mixed product was reduced as described for (VI), and the reduction product fractionally sublimed at 200°/0·03 mm. The less volatile amine formed bright red crystals, m. p. 227° alone or mixed with (VII) : the more volatile amine (probably the 8-amino-derivative) formed yellow crystals, m. p. 183°.

2-*Carboxy*-3-*pyridyl Phenyl Sulphide* (X).—This sulphide was prepared from the diazotised acid (IX) (6·3 g.) (Sucharda, *Ber.*, 1925, **58**, 1728) under the same conditions as were used for the preparation of (II) from the acid (I). The cautious addition of acetic acid to the final filtered solution to obtain pH 5 caused however a copious precipitate consisting apparently of a double sodium hydrogen salt, colourless plates (5·6 g.), m. p. 318° (decomp.), from ethanol (Found : C, 59·6; H, 3·4; N, 5·6. $C_{24}H_{17}O_4N_2S_2Na$ requires C, 59·5; H, 3·5; N, 5·8%). This recrystallised salt, when treated with glacial acetic acid, gave the pure cream-coloured *sulphide* (X), m. p. 162° (decomp.) (Found : C, 62·1; H, 4·2; N, 5·95. $C_{12}H_9O_2NS$ requires C, 62·3; H, 3·9; N, 6·05%). Alternatively, the sulphide was obtained by crystallisation of the crude sodium salt from acetic acid, a less soluble crop of diphenyl disulphide being rejected.

The sulphide, when heated above its m. p., underwent a ready decarboxylation to the liquid phenyl 3-pyridyl sulphide, which was volatile in steam and was characterised as its *picrate*, yellow leaflets, m. p. 126°, from water (Found : C, 49·7; H, 3·05; N, 13·6. $C_{11}H_9NS,C_6H_3O_7N_3$ requires C, 49·1; H, 2·9; N, 13·5%).

9-*Thia*-4-*aza-anthrone* (XI).—This compound was prepared from the sulphide (X) (0·5 g.) as (III) was prepared from (II) : the final precipitate, when sublimed at 180—190°/0·07 mm., gave the cream-coloured *anthrone* (XI) (0·27 g., 59%), m. p. 224° (Found : C, 67·3; H, 3·3; N, 6·5. $C_{12}H_7ONS$ requires C, 67·6; H, 3·3; N, 6·6%). It gives a yellow solution in sulphuric acid.

On one occasion the anthrone (XI) was obtained by the action of phosphorus oxychloride on the sulphide (X) : the conditions require delicate adjustment, however, and the above method is preferable.

When cyclisation of (X) was attempted by treatment with sulphuric acid at 140—150° for 4 hr., only sulphonation occurred, with the formation of 2-*carboxy*-3-*pyridyl* p-*sulphophenyl sulphide*, pale yellow leaflets, m. p. 262° (decomp.), from water (Found : C, 45·8; H, 2·9; N, 4·5. $C_{12}H_9O_5NS_2$ requires C, 46·3; H, 2·9; N, 4·5%). (It is assumed that sulphonation has occurred in the *para*-position to the sulphur atom.)

The *methiodide* of the anthrone (XI), prepared as previously described, crystallised from hot water in orange rods and from cold water in yellow needles, both forms becoming scarlet on drying (Found : C, 43·7; H, 2·8; N, 3·75. $C_{13}H_{10}ONIS$ requires C, 43·9; H, 2·8; N, 3·9%); the methiodide decomposes at 181° with reversion to the anthrone (XI). The *methochloride*, prepared as before, and recrystallised from ethanol–ether, formed a sesquihydrate, yellow needles which readily decompose to the anthrone at *ca.* 150—160° (Found : C, 54·0; H, 4·5; N, 5·1. $C_{13}H_{10}ONCl,1{\cdot}5H_2O$ requires C, 53·7; H, 4·5; N, 4·8%). The readiness with which these two quaternary salts lose methyl halide when heated is noteworthy.

9-*Thia*-4-*aza-anthrone* 9 : 9-*Dioxide*.—This *sulphone*, prepared as was (IV), was obtained as colourless needles, m. p. 204°, from ethanol (Found : C, 58·8; H, 3·2; N, 6·0. $C_{12}H_7O_3NS$ requires C, 58·8; H, 2·85; N, 5·7%). For infra-red data, see below.

2-*Carboxy*-3-*pyridyl* p-*Nitrophenyl Sulphide* (XII; R = NO_2).—A solution of the diazotised acid (IX) (4·2 g.) was added rapidly to a boiling solution of *p*-nitrothiophenol (5·2 g., 1·1 mols.) in 5% aqueous sodium hydroxide (200 c.c.). When nitrogen evolution ceased, the solution was cooled, filtered, and acidified with hydrochloric acid. The precipitated *sulphide* (XII; R = NO_2) (7·0 g., 92%) gave yellow needles, m. p. 190° (decomp.), after recrystallisation from acetic acid and ethanol in turn (Found : C, 52·2; H, 3·1; N, 9·7. $C_{12}H_8O_4N_2S$ requires C, 52·2; H, 2·9; N, 10·1%). The sulphide, when heated above its m. p., smoothly formed p-*nitrophenyl* 3-*pyridyl sulphide*, pale yellow needles, m. p. 115°, from ethanol (Found : C, 56·8; H, 3·2; N, 12·0. $C_{11}H_8O_2N_2S$ requires C, 56·9; H, 3·4; N, 12·1%).

Nitration of the Anthrone (XI).—This anthrone (400 mg.) was nitrated as was (III), with potassium nitrate (240 mg.), the complete mixture being kept at 30—35° for 15 min.; the initial deep yellow colour faded almost completely, and a green fluorescence developed. The final yellow precipitate (420 mg.) was collected, washed, dried, and extracted repeatedly with boiling ethanol. The insoluble residue (353 mg.), after sublimation at 200°/0·03 mm. and recrystallisation from acetic acid, gave 6-*nitro*-9-*thia*-4-*aza-anthrone* (XIII), pale yellow leaflets m. p. 298° (Found : C, 55·9; H, 2·4; N, 10·8. $C_{12}H_6O_3N_2S$ requires C, 55·8; H, 2·3; N, 10·8%).

The ethanolic extracts on evaporation gave a residue (63 mg.) which, recrystallised from

ethanol, furnished the bright yellow 8-*nitro*-derivative (XIV), m. p. 249° (Found: C, 56·1; H 2·6; N, 10·7. $C_{12}H_6O_3N_2S$ requires C, 55·8; H, 2·3; N, 10·8%).

Reduction of 6-*Nitro*-9-*thia*-4-*aza-anthrone* (XIII).—(*a*) Stannous chloride (1 g.) in concentrated hydrochloric acid (15 c.c.) was added to the anthrone (XIII) (0·3 g.) in acetic acid (20 c.c.). The mixture was then kept at 50—60° for 1 hr., then made strongly alkaline with aqueous sodium hydroxide, and the reddish-brown precipitate (0·13 g.) collected, washed, and dried. Sublimation at 220°/0·03 mm. slowly gave the 6-*amino*-derivative (XV) as a scarlet microcrystalline powder, m. p. 246°; alternatively, recrystallisation from acetic acid gave brownish-red rhombs, also m. p. 246° (Found: C, 63·4; H, 3·3; N, 12·0. $C_{12}H_8ON_2S$ requires C, 63·2; H, 3·5; N, 12·3%).

(*b*) Granulated tin (270 mg.) and concentrated hydrochloric acid (*ca.* 0·1 c.c.) were added in turn to a suspension of the anthrone (150 mg.) in 70% acetic acid (10 c.c.) which was then kept at 90° for 1 hr.; a clear pale yellow solution remained. This was worked up as in (*a*). Sublimation at 175—180°/0·03 mm. readily gave 6-*amino*-9 : 10-*dihydro*-9-*thia*-4-*aza-anthracene* (XVI) (50 mg., crude), m. p. 159·5—160° (Found: C, 67·3; H, 4·9; N, 13·1. $C_{12}H_{10}N_2S$ requires C, 67·3; H, 4·7; N, 13·1%). A very small residue of the amino-anthrone (XV) remained unsublimed.

The 6-amino-anthrone (XV) when similarly treated also yielded (XVI), m. p. and mixed m. p. 159—160°.

Reduction of 2-*Carboxy*-3-*pyridyl* p-*Nitrophenyl Sulphide* (XII; R = NO_2).—Concentrated hydrochloric acid was added dropwise to the sulphide (2 g.) and granulated tin (2 g.) in ethanol (20 c.c.), which was kept at 40—50° until all the tin had dissolved. The solution was concentrated in a vacuum, mixed with water, filtered, and saturated with hydrogen sulphide; precipitated sulphides were collected, and the filtrate was acidified with hydrochloric acid, evaporated to small volume, and whilst hot diluted with acetone until a turbidity became just apparent. The solution on cooling deposited the p-*aminophenyl* 2-*carboxy*-3-*pyridyl sulphide hydrochloride* (XII; R = NH_2,HCl), pale cream-coloured needles, m. p. 195° (decomp.) after crystallisation from ethanol–ether (Found: C, 50·7; H, 4·2; N, 9·6. $C_{12}H_{10}O_2N_2S$,HCl requires C, 50·9; H, 3·9; N, 9·9%).

This amino-compound underwent ready deamination under conditions analogous to those employed by Brewster and Page (*J. Amer. Chem. Soc.*, 1939, **61**, 2418). A solution of the hydrochloride (500 mg.) was diazotised, added to hypophosphorous acid (10 c.c.), and set aside overnight at 1—2°. On adjustment of the pH to 4, the pale yellow sulphide (X) (220 mg.) was precipitated; after recrystallisation from aqueous ethanol, it had m. p. 162° (decomp.), alone and mixed with the former sample.

A solution of the above hydrochloride (140 mg.), diethylaniline (0·2 c.c.), and ethyl chloroformate (0·1 c.c.) in ethanol (50 c.c.) was boiled under reflux for 15 min., concentrated, and diluted with water. The p-*ethoxycarbonylaminophenyl* 2-*carboxy*-3-*pyridyl sulphide* (XII; R = ·NH·CO_2Et) which separated crystallised from aqueous ethanol as cream-coloured crystals, m. p. 179—180° (decomp.) (Found: C, 56·8; H, 4·6; N, 9·0. $C_{15}H_{14}O_4N_2S$ requires C, 56·6; H, 4·4; N, 8·8%). Attempts to cyclise this compound failed, although the comparable cyclisation of other urethanes has been recorded (cf. Walls, *J.*, 1947, 67).

p-*Carboxyphenyl* 2-*Carboxy*-3-*pyridyl Sulphide* (XVII).—A solution of the diazotised acid (IX) (1·05 g.) was added to boiling 20% aqueous sodium hydroxide (15 c.c.) to which methyl *p*-mercaptobenzoate (1·3 g.) had been added immediately before. The cooled solution was acidified to pH 3 with hydrochloric acid, and the precipitated *sulphide* (XVII) (1·4 g., 67%), after recrystallisation from dioxan, gave colourless crystals, m. p. 215° (decomp.) (Found: C, 57·1; H, 3·3; N, 5·3. $C_{13}H_9O_4NS$ requires C, 56·8; H, 3·3; N, 5·1%). The use of *p*-mercaptobenzoic acid on one occasion gave (XVII) in low yield, but on all others gave an unidentified solid of high m. p.

The sulphide, when heated above its m. p., underwent smooth decarboxylation to p-*carboxyphenyl* 3-*pyridyl sulphide* (XVIII), crystals, m. p. 173·5—174·5° from aqueous ethanol (Found: C, 62·4; H, 3·9; N, 5·9. $C_{12}H_9O_2NS$ requires C, 62·3; H, 3·9; N, 6·05%).

9-*Thia*-1-*aza-anthrone Methochloride*.—This salt, which has not previously been described, was prepared from the corresponding methiodide (Mann and Reid, *loc. cit.*) precisely as the above 2-aza- and 4-aza-analogues, and obtained as buff-coloured hygroscopic needles, m. p. 226° (decomp.), of the *hemihydrate* from methanol–ether (Found: C, 57·4; H, 4·2. $C_{13}H_{10}ONClS,0{\cdot}5H_2O$ requires C, 57·3; H, 4·1%).

Infra-red Investigation of 9-*Thia*-2-*aza-anthrone* 9 : 9-*Dioxide* (IV) *and its* 4-*Aza-isomeride*.—These compounds were identified as sulphones by the method already described (Mann and

Reid, *loc. cit.*), based on the fact that sulphones normally have strong absorption bands in the regions of 1340—1295 and 1160—1120 cm.$^{-1}$, whereas sulphoxides show a single strong absorption band at 1060—1030 cm.$^{-1}$. The compound (IV) had two strong bands at 1299 and 1160 cm.$^{-1}$, and the 4-aza-compound similarly at 1295 and 1164 cm.$^{-1}$ (cf. the 1-aza-isomer, which showed bands at 1315 and 1165 cm.$^{-1}$). This provides very strong evidence that the two compounds were sulphones and not pyridine oxide sulphoxides. The compound (IV) and the 4-aza-isomer also showed a considerably weaker band at 1157 cm.$^{-1}$, which does not however indicate a sulphoxide group.

We are greatly indebted to Dr. Joan A. Reid for a preliminary investigation of the synthesis of compounds (II) and (III), to Mr. O. D. Standen for the therapeutic tests, and to the Medical Research Council for a grant (S. K.).

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The Kinetics and Mechanisms of Addition to Olefinic Substances. Part I. Rearrangement accompanying Addition of Hypochlorous Acid to Allyl Chloride.

By P. B. D. DE LA MARE and J. G. PRITCHARD.

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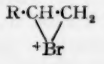
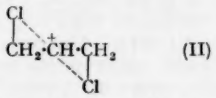
Hypochlorous acid adds to allyl chloride at high dilutions in aqueous solution in the presence of perchloric acid and silver perchlorate to give a mixture of 1 : 3-dichloropropan-2-ol (30%) and 2 : 3-dichloropropan-1-ol (70%). Under the stated conditions, the kinetic measurements make it probable that the electrophilic reagent which initiates the addition is Cl^+ or H_2OCl^+. Previous workers have recorded similar proportions of the isomeric dichlorohydrins under conditions in which Cl_2 or Cl_2O are probably the functioning reagents. By using ^{36}Cl in the allyl chloride, it has been shown that a small proportion of the chlorine which is found in the 2-position of 2 : 3-dichloropropan-1-ol is derived by migration of the chlorine atom in the original allyl chloride. Approximately 88% of the 2 : 3-dichloropropan-1-ol must be derived from an intermediate which is not symmetrical about $C_{(2)}$. The significance of these observations is discussed.

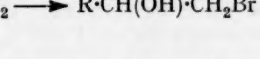
THE direction of addition to allyl chloride appears to vary considerably with the reagent. Even if reagents which add by free-radical reactions (*e.g.*, hydrogen bromide in the presence of peroxides) are neglected, the situation is still not immediately clear. Hydrogen chloride adds to form 1 : 2-dichloropropane, and hydrogen iodide gives 1-chloro-2-iodopropane (Kharasch, Kleiger, and Mayo, *J. Org. Chem.*, 1939, **4**, 430, 433; Kharasch, Norton, and Mayo, *J. Amer. Chem. Soc.*, 1940, **62**, 81). These results accord with the view that the CH_2Cl group releases electrons to an adjacent ethylenic system, an effect which would now normally be attributed to hyperconjugation. They also accord with the electron-releasing power of the CH_2Cl group, as shown in aromatic substitution by the predominantly *ortho-para*-directing character of the group, recently discussed by Ingold and Shaw (*J.*, 1949, 575) and by the greater reactivity (in *para*-substitution) of benzyl chloride than of benzene to electrophilic halogens (Swindale, Swedlund, and Robertson, *J.*, 1950, 812).

In the case of hypochlorous acid, on the other hand, it has been recorded that addition to allyl chloride gives predominantly 2 : 3-dichloropropan-1-ol, and this reaction was carefully investigated by Lennart Smith (*Z. physikal. Chem.*, 1918, **92**, 739). Using a kinetic method for the analysis of the product, he showed that the mixture of dichlorohydrins produced in the reaction contained about 70% of the 2 : 3-dichloro-compound. The latter result is clearly anomalous, since hypochlorous acid is generally considered to react in the sense $\overset{\delta+}{Cl}\text{–}\overset{\delta-}{OH}$, as is confirmed, for example, by addition of this reagent to propylene to give predominantly 1-chloropropan-2-ol.

An explanation of this difficulty has now been sought in the more detailed consideration of the course of addition of hypochlorous acid to allyl chloride. The attack of an electrophilic reagent, Cl–X, on an olefinic substance, R·CH:CH_2, is often considered to proceed through the intermediate stage of a carbonium ion, $^+$CHR·CH_2Cl. The fact that the completion of addition can be shown, by stereochemical observations in selected cases, to involve attack by a nucleophilic reagent on the side opposite from the attached halogen, is taken to imply interaction between the halogen and the carbonium ionic centre. Roberts and Kimball (*J. Amer. Chem. Soc.*, 1937, **59**, 947) suggested, for addition of bromine, that "bromonium" structures such as (I) contributed to the hybrid carbonium ions. Lucas and Gould (*ibid.*, 1941, **63**, 2541) wrote similar "chloronium" structures to explain *trans*-addition of chlorine to the isomeric but-2-enes.

Similar intermediates are considered (cf. Winstein and Buckles, *ibid.*, 1942, **64**, 2787; Winstein and Grunwald, *ibid.*, 1948, **70**, 828) to be concerned in substitution reactions of 1 : 2-dihalides. The exact nature of these complexes has been a matter of some controversy

(I)  (II) 

(cf., for example, Winstein and Ingraham, *ibid.*, 1952, **74**, 1160), but this need not concern us for the moment. The crucial point is the possibility, which arises in any case of such interaction between a substituent and an adjacent carbonium centre, that subsequent reactions with nucleophilic reagents may occur in either of the two possible ways:  and R·CHBr·CH_2·OH. Furthermore, the symmetrical relation of the chlorine atoms in the similar intermediate (II) which might be derived from allyl chloride suggests that an experimental test of the intervention of an intermediate of this sort in the formation of 2 : 3-dichloropropan-1-ol from allyl chloride might be obtained by the isotopic labelling of the organic chloride.

In seeking the best experimental conditions for study of the reaction between hypochlorous acid and allyl chloride, we have been guided by kinetic considerations. The addition of hypochlorous acid to olefinic substances, under essentially neutral conditions, has been examined extensively by Shilov and his co-workers (cf. Shilov, Kupinskaya, and Yasnekow, *Doklady Akad. Nauk S.S.S.R.*, 1951, **81**, 435), as well as by Soper, Israel, and their co-workers (cf. Israel, Martin, and Soper, *J.*, 1950, 1282; Reeve and Israel, *J.*, 1952, 2327). The results indicate that the kinetic forms are extremely elaborate under these conditions. These complexities persist into more strongly acid conditions; but preliminary studies (de la Mare, Hughes, and Vernon, *Research*, 1950, **3**, 242) indicated that in very dilute aqueous solution, at pH less than 2, and in the presence of silver perchlorate to remove chloride ions, conditions exist under which Cl^+ and $ClOH_2^+$ are almost certainly the kinetic intermediates initiating the addition. These conditions have therefore been used in the present study, since in these circumstances an intermediate such as (II) is very likely to be involved.

Experimental

Materials.—Commercial allyl chloride was shaken with saturated aqueous potassium iodide, then with a little aqueous sodium nitrite, washed with water, dried, and fractionated, then having b. p. 44·4—44·7°, n_D^{25} 1·4120. To label this material with ^{36}Cl, the allyl chloride (100 ml.) was refluxed for 3 days with acetone and Li^{36}Cl, prepared from H^{36}Cl obtained from a sample of K^{36}Cl supplied by A.E.R.E., Harwell. The product was fractionated, and the material of b. p. 45—50° was washed repeatedly with ice-cold water to remove acetone, dried (Na_2SO_4), and fractionated, giving a material of b. p. 46°, n_D^{25} 1·4122.

Hypochlorous acid was prepared from chlorine water and mercuric oxide in the usual way (cf. de la Mare, Ketley, and Vernon, *J.*, 1954, 1290).

1 : 3-Dichloropropan-2-ol and 2 : 3-dichloropropan-1-ol were prepared as described elsewhere (de la Mare and Pritchard, *J.*, 1954, 1644). They were shown to be pure by kinetic

analysis; it is to be noted that this, as far as the authors are aware, is the only method so far established for estimating the purity of these isomeric compounds.

Reaction of Hypochlorous Acid with Allyl Chloride.—Allyl chloride (75 ml.) labelled with ^{36}Cl was dissolved in a solution (*ca.* 90 l., in a 100-l. flask) containing silver perchlorate (0·02M) and perchloric acid (0·02M). To this was added standardised 0·1M-hypochlorous acid solution (in total, 2·6 l.), at such a rate that the concentration of hypochlorous acid in the reaction mixture was always below 0·001M. On completion of the reaction, the excess of allyl chloride was removed by passage of air through the solution, and was then freed from acid by bubbling through saturated sodium carbonate solution, and from water by passage through anhydrous calcium chloride. The allyl chloride was then collected in traps cooled in liquid air.

The reaction mixture was saturated with ether (*ca.* 5 l.), and then with anhydrous sodium sulphate (*ca.* 14 kg.). The ether layer was removed, and the aqueous solution was further extracted several times (in total about 15 l. of ether). The ether extracts were dried (Na_2SO_4) and fractionated. After removal of the ether, there were obtained, with negligible intermediate fractions, (*a*) 1 ml., b. p. 70—81°/19·5 mm., which on redistillation at ordinary pressure gave *ca.* 0·1 g., b. p. 94—96°, n_D^{25} 1·4310 [the remainder (*ca.* 1 g.) distilled almost entirely over the range 176—182°], (*b*) 3 g., b. p. 81—82°/19·5 mm., n_D^{25} 1·4808, and (*c*) 12·5 g., b. p. 82—84°/19·5 mm., n_D^{25} 1·4815. Fractions (*b*) and (*c*) were combined for analysis as dichlorohydrin mixture (52% yield, based on the hypochlorous acid taken) (Found: C, 27·6; H, 4·9. Calc. for $C_3H_6OCl_2$: C, 27·9; H, 4·7%). This sample was also analysed kinetically, as discussed below, and contained 30% of 1 : 3-dichloropropan-2-ol and 70% of 2 : 3-dichloropropan-1-ol.

The dichlorohydrin mixture (15 g.) was allowed to react with 0·5N-sodium hydroxide (75 ml., being in excess by 8% of the amount of 1 : 3-dichloropropan-2-ol present) for 15 min. at 0°. The mixture was then extracted with ether, and the extract was dried (Na_2SO_4) and fractionated. After removal of the ether and epichlorohydrin, there were recovered 6 g. (60% recovery), n_D^{25} 1·4819, b. p. 85—86°/19·5 mm. (Found: C, 27·9; H, 4·8. Calc. for $C_3H_6OCl_2$: C, 27·9; H, 4·7%). Kinetic analysis then revealed, within the experimental error (*ca.* 1 unit %), no 1 : 3-dichloropropan-2-ol.

The above labelled 2 : 3-dichloropropan-1-ol (3·70 g.) was diluted with 8·04 g. of inactive, pure 2 : 3-dichloropropan-1-ol, and converted into epichlorohydrin by reaction with N-sodium hydroxide at 0° for 19 hr. The product was extracted with ether, and the extract was dried and fractionated, giving 2 g., b. p. 114—115°, together with some material of high b. p. (cf. de la Mare and Pritchard, *loc. cit.*). Refractionation gave pure epichlorohydrin (1·2 g.; b. p. 114—114·5°/760 mm., n_D^{25} 1·4358) (Found: C, 38·9; H, 5·7. Calc. for C_3H_5OCl: C, 38·9; H, 5·4%).

Known weights of the various samples were dissolved in alcohol and their radioactivity was determined by the technique usual for liquid samples (cf. de la Mare and Pritchard, *loc. cit.*). The results are shown in Table 1.

TABLE 1. *Counting data for samples from reaction of allyl chloride with hypochlorous acid.*

No.	Sample	Dilution ratio	Concn. of solution (g./10 ml.)	Mol. wt.	Count */ min.	Count/min. (corr. for mol. wt. and dilution)
1	Allyl chloride	1·00	0·6309	76·5	437·8	531 ± 5
2	Allyl chloride (recovered after reaction)	1·00	0·8155	76·5	566·8	532 ± 5
3	2 : 3-Dichloropropan-1-ol (recovered from reaction)	1·00	0·7342	129·0	310·8	546 ± 6
4	2 : 3-Dichloropropan-1-ol (diluted)	3·17	1·014	129·0	134·9	545 ± 8
5	Epichlorohydrin from 2 : 3-dichloropropan-1-ol	3·17	1·265	92·5	220·5	512 ± 7

* Counts are corrected for background (*ca.* 10 per min.). The probable errors are calculated on the basis of random fluctuations in the rate of counting. The first two results are strictly comparable, being done together; the next three are similarly comparable. The difference between samples 1—2, and 3—4 is probably slightly greater than the counting error, and probably results from a slight difference in counting conditions, since the two sets of counts were done at different times, and it is difficult to reproduce precisely the voltage-setting on the counter.

Kinetics of Addition of Hypochlorous Acid to Allyl Chloride.—This has been studied only in a very preliminary way, by the following method. Aqueous solutions of (i) allyl chloride and (ii) hypochlorous acid, perchloric acid, and silver perchlorate were mixed at 25° and transferred

to a blackened flask (200 ml.), from which samples could be removed through a narrow, normally stoppered tube leading to the bottom of the flask. The latter was also attached to an aspirator (200 ml.) also containing the reacting solution at 25°; so that, when samples were removed for titration, the air replacing the removed solution was that in equilibrium with the reacting solution, and hence the concentration of reactants in the flask did not change appreciably as the result of volatility or diffusion losses. The samples were quenched in potassium iodide solution saturated with nitrogen, and were titrated under nitrogen with 0·001N-sodium thiosulphate, the starch–sodium glycollate indicator being used. The initial concentration of allyl chloride was determined by running a sample into a known excess of hypochlorous acid to which hydrogen chloride was added. The liberated chlorine reacted instantaneously with the allyl chloride, and the excess of chlorine was determined, after addition of potassium iodide, by back-titration in the usual way. The following are results at 25° for the reaction of 0·0085M-allyl chloride with 0·0044M-hypochlorous acid in the presence of 0·021M-perchloric acid and 0·020M-silver perchlorate; these conditions resemble closely those used in the product analyses.

Time (min.)	0·00	19·5	39·7	43·8	54·3	66·8	83·6	∞
Titre (ml. of 0·001N-$Na_2S_2O_3$)	5·62	4·63	3·90	3·65	3·27	2·88	2·50	0·00
10^3k_1 (min.$^{-1}$)	—	9·94	9·86	9·84	9·97	9·66	9·69	—

The reaction is clearly of the first order with respect to hypochlorous acid. If silver perchlorate is omitted, the reaction is very fast (k_1 = *ca.* 1 min.$^{-1}$). Acid-catalysis is demonstrated by the following results, which apply to rather higher concentrations (*ca.* 0·02M) of allyl chloride, reacting with 0·0005M-hypochlorous acid in the presence of 0·02M-silver perchlorate: with 0·01M-$HClO_4$, 10^3k_1 = 16 min.$^{-1}$; with 0·030M-$HClO_4$, 10^3k_1 = 33 min.$^{-1}$.

Reaction of Allyl Chloride with Silver Perchlorate.—Silver perchlorate was added to the reaction mixture to minimise reaction through free chlorine. It was necessary to check, therefore, that silver perchlorate did not interfere with addition by catalysing hydrolysis of the allyl chloride. Below are the results obtained in following the decrease of concentration of silver ion at 25°, in a solution containing 0·02M-allyl chloride, 0·02M-silver perchlorate, and 0·01M-perchloric acid. Samples were used for titration, at intervals, potentiometrically, of 10·0-ml. samples of 0·0454N-sodium chloride.

Time (min.)	0·0	65	110	165	∞
Ag^+ (M)	0·0184	0·0180	0·0178	0·0175	0·0000
10^3k_1 (min.$^{-1}$)	—	0·35	0·32	0·32	—

The first-order rate-coefficient for the hydrolysis is less than 4% of the first-order rate-coefficient for the addition under the conditions used for the product analysis, and therefore the former reaction is considered to interfere negligibly with the latter.

Kinetic Analysis of Chlorohydrin Mixtures.—This aspect of the present study was greatly facilitated by the preliminary investigation by G. J. Pritchard and C. K. Ingold (personal communication). In a typical experiment, to 100 ml. of 0·04165M-alkali at 25° was added an exactly equivalent amount (0·5372 g.) of the mixed dichlorohydrins. At intervals, 10-ml. samples were added to 10 ml. of 0·0538N-hydrochloric acid, and back-titrated with 0·04165N-alkali. A correction was applied for the dilution of the solution by the added dichlorohydrin.

Time (min.)	0·0	4·6	16·2	34·9	56·1	100·9	123·6	∞
Titre (ml.)	2·90	6·03	6·72	7·49	8·15	9·22	9·60	12·84
$1/(a - x)$	0·1000	0·1468	0·1634	0·1869	0·2132	0·2762	0·3086	—

The expression for bimolecular reaction for pure single chlorohydrin is: $k_2 = x/(a - x)at$, or $1/(a - x) = k_2t + 1/a$. The plot of $1/(a - x)$ against t gives a straight line of slope k_2 and intercept $1/a$ on the $1/(a - x)$ axis. For a mixture of two compounds differing considerably in reaction rate, the plot of $1/(a - x)$ against t may be used to find the proportion of each compound present. Application of this treatment to the above data gives a straight line of slope k_2 = 0·32 l. mole^{-1} min.$^{-1}$. This value agrees with that recorded elsewhere (de la Mare and Pritchard, *loc. cit.*) for pure 2 : 3-dichloropropan-1-ol. The intercept on the $1/(a - x)$ axis gives a value of a = 0·0292 mole l.$^{-1}$. The ratio of a obtained by extrapolation and a calculated from the total weight of dichlorohydrin taken demonstrates that 70% of the starting material is 2 : 3-dichloropropan-1-ol. The remainder is isomeric 1 : 3-dichloropropan-2-ol, which is about 200 times more reactive than its isomer and was therefore destroyed to the extent of at least 99% before the first experimental point was reached. Separate experiments at 0°, in which the reaction constant could be calculated, confirmed that the reactive material was the isomeric dichlorohydrin. Synthetic mixtures of dichlorohydrins, similar in composition to the above,

were analysed and gave results which checked with their known compositions within 1%. This method depends for its accuracy on the fact that, of the two isomers, one is considerably more reactive than the other (*e.g.*, by a factor of about 100).

Discussion

(a) *Kinetics of Addition of Hypochlorous Acid to Allyl Chloride.*—Elsewhere (de la Mare, Hughes, and Vernon, *loc. cit.*), preliminary evidence has been presented showing that hypochlorous acid may, under controlled kinetic conditions, add to olefinic substances by way of the chlorinium ion, Cl^+. The evidence was derived from the observation that, in the absence of chloride ions, hypochlorous acid adds to such compounds as allyl ethyl ether and allyl fluoride at a rate, which, though subject to acid catalysis, is nearly independent, at low concentrations, of the nature of the olefinic material and its concentration.

More recently, a detailed examination of the kinetically similar reaction between hypochlorous acid and aromatic substances (de la Mare, Ketley, and Vernon, *loc. cit.*) has thrown further light on the complex kinetic behaviour of these systems. Very low concentrations ($\gtrsim$ M/1000-hypochlorous acid) must be used to prevent part of the chlorination proceeding through Cl_2O. The full kinetic form, at concentrations of aromatic compound large enough to remove Cl^+ as soon as it is formed, is found to be:

$$-\mathrm{d[ClOH]}/\mathrm{d}t = k[\mathrm{ClOH}] + k'[\mathrm{ClOH}][\mathrm{H^+}] + k''[\mathrm{ClOH}][\mathrm{H^+}][\mathrm{ArH}]$$

in which the first two terms of the right-hand side are considered to represent the rate of heterolytic fission of ClOH and $ClOH_2^+$ respectively, giving Cl^+, and the last term the rate of attack of $ClOH_2^+$ on the aromatic compound.

A difficulty in interpreting the coefficient k'' arises because unsaturated compounds (including aromatic materials) form complexes with the silver ion which must be added to prevent reaction proceeding through Cl_2. This difficulty is more serious in the case of the reactions of the olefins with hypochlorous acid than for aromatic compounds, because on the whole the equilibria $A + Ag^+ \rightleftharpoons [A{\cdot}Ag]^+$ lie further to the right for the former class of substances. So far, a full kinetic investigation of the reactions of the olefinic substances in which we are interested has not been completed; but the preliminary data presented here show the following: (*a*) under the specified conditions (high dilution, Ag^+ present), the rate is always of the kinetic form $-\mathrm{d[ClOH]}/\mathrm{d}t \propto [\mathrm{ClOH}]$; (*b*) with sufficiently high silver-ion concentration, the rate becomes substantially independent of this concentration; (*c*) the magnitudes of the rates are similar to those obtained for the analogous reaction of, *e.g.*, phenol (cf. de la Mare, Ketley, and Vernon, *loc. cit.*); (*d*) the reaction is catalysed by acids. Subsidiary experiments showed that the concomitant hydrolysis of allyl chloride, catalysed by Ag^+, is slow and affects negligibly the addition reaction.

It is concluded, therefore, in agreement with de la Mare, Hughes, and Vernon (*loc. cit.*) that addition of hypochlorous acid follows, under these conditions, the same general pattern as substitution of aromatic compounds by this reagent; and that, under the conditions used for the product analysis, Cl^+ and $ClOH_2^+$ both contribute to the initiation of the addition.

(b) *Products resulting from Addition of Hypochlorous Acid to Allyl Chloride.*—The silver-ion-catalysed hydrolysis of allyl chloride, leading to allyl alcohol and thence to monochlorohydrin, appears, from its measured rate, to contribute less than 4% to the measured process. We were unable to detect any of the possible products (*e.g.*, $CH_2Cl{\cdot}CH{:}CHCl$ or $CH_2{:}CCl{\cdot}CH_2Cl$) of unimolecular elimination through the carbonium ions (*e.g.*, $CH_2Cl{\cdot}{}^+CH{\cdot}CH_2Cl$ or $^+CH_2{\cdot}CHCl{\cdot}CH_2Cl$) which might be considered as possible intermediates in the addition process. The only ether-extractable material recoverable in identifiable quantity from the reaction was a mixture of dichlorohydrins. The total yield (*ca.* 50%) is considered satisfactory in view of the great dilution at which the experiment was necessarily performed.

Kinetic analysis of the mixture of chlorohydrins obtained in various experiments carried out by us and by other workers gave the results shown in Table 2.

The isomeric product ratio does not seem to vary greatly with the nature of the electro-

philic reagent which is concerned in the rate-determining attack on the double bond. The formation of an excess of 2 : 3-dichloropropan-1-ol may be taken, therefore, to be characteristic of an addition in which Cl^+ is supplied by an electrophilic reagent, and the solvent then provides the hydroxyl group to complete the addition.

TABLE 2. *Products from addition of hypochlorous acid to allyl chloride in water.*

Allyl chloride (M)	ClOH (M)	$AgClO_4$ (M)	$HClO_4$ (M)	Probable reagent	2 : 3-Dichloropropan-1-ol (%) *	Ref.
0·01	0·001	0·02	0·02	Cl^+, $ClOH_2^+$	70	This work
0·001	0·001	0·02	0·02	$ClOH_2$, Cl^+	68·5	,,
ca. 1	0·1	0·0	*ca.* 0·02	Cl_2O, Cl_2	66·5	,,
0·001	0·001	0·0	0·05	Cl_2, Cl_2O	67·5	,,
Allyl chloride + hypochlorite					68	Lennart Smith (*loc. cit.*)
Allyl chloride + concentrated chlorine water				Cl_2, Cl_2O	68	Ingold and G. J. Pritchard (personal communication)

* Accuracy estimated as ±1%.

(c) *Addition of Hypochlorous Acid to* $CH_2{:}CH{\cdot}CH_2{\cdot}^{36}Cl$.—When considering the results of Table 1, the following points should be noted. The excess of allyl chloride, recovered after completion of the reaction, maintained in full its radioactivity. This shows that radioactive dilution of the product does not arise from some exchange between allyl chloride and the reactants in the solution. A corollary is that the stage in which the Cl^+ is added to $C_{(1)}$ to form a carbonium cation is not reversible, so that there is no need to consider the possible reversibility of formation of a symmetrical cation, $[Cl{\cdot}CH_2{\cdot}\overset{+}{C}H{\cdot}CH_2{\cdot}^{36}Cl]$. Secondly, the writers have shown (*loc. cit.*) that when $HO{\cdot}CH_2{\cdot}CHCl{\cdot}CH_2{\cdot}^{36}Cl$ is treated with alkali, the recovered epichlorohydrin retains, within experimental error, all the ^{36}Cl. Hence the diminution in specific activity of the epichlorohydrin (Table 1) is not the result of extraneous exchange during working-up of the products.

We consider, therefore, that the results show that some exchange occurs during the addition, and hence that some of the 2 : 3-dichloropropan-1-ol comes by migration of ^{36}Cl to $C_{(2)}$ in an effectively symmetrical intermediate, $[Cl{\cdot}CH_2{\cdot}\overset{+}{C}H{\cdot}CH_2{\cdot}^{36}Cl]$, written here without specifying interaction between the chlorine substituents and the carbonium ionic centre. If all the reaction proceeded by this route, then the specific activity of the epichlorohydrin isolated from the 2 : 3-dichloropropan-1-ol would have fallen from 546 counts/min. to 273 counts/min. That the observed value was 512 counts/min. indicates that not more than 12% could have been formed through such an intermediate. The remainder must be derived by some other route.

The following conclusions may then be drawn: First, the "unusual" orientation in the reaction of hypochlorous acid with allyl chloride has been confirmed. Secondly, this orientation persists under conditions in which Cl^+ and $ClOH_2^+$ are almost certainly the rate-determining electrophilic reagents. Thirdly, a small but significant amount of the 2 : 3-dichloropropan-1-ol comes from an intermediate such as (II) (p. 3911) in which the entering and the already present chlorine substituents have become effectively equivalent. Fourthly, the major amount of the 2 : 3-dichloropropan-1-ol does not come from such an intermediate, or from any cation of life long enough to allow the two chlorine atoms to become equivalent, as, for example, in a process of dynamic equilibrium between two forms:

In the accompanying paper, these conclusions are amplified by comparison with data relating to reactions of hypochlorous acid with other olefinic substances, and to the reactions of three-membered ring-compounds and intermediates.

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Aromatic Keto-enols. Part III. Some Heterocyclic Quinols.*

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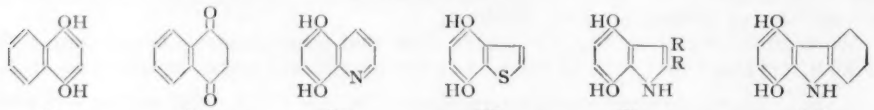
Alkylated 4 : 7-dihydroxyindoles can be prepared by the Bischler synthesis. Attempts to tautomerise 5 : 8-dihydroxyquinoline, 4 : 7-dihydroxythionaphthen, 4 : 7-dihydroxy-2 : 3-dimethylindole, and 1 : 3- and 2 : 3-dihydroxynaphthalene were unsuccessful.

In previous papers * it has been shown that 1 : 4-dihydroxynaphthalene, 1 : 4-dihydroxyanthracene, and some related compounds can isomerise to diketones on fusion *in vacuo*, *e.g.*, (I) ⟶ (II). In this tautomeric change the gain in bond energies in the conversion enol → keto is counterbalanced by the lower resonance energy of the resulting diketone. That the balance is fine is evident from the fact that a diketone cannot be obtained unless both carbonyl groups are conjugated with the benzene ring (*e.g.*, as in II). Thus diketones could not be isolated by fusion of 1 : 3- or 2 : 3-dihydroxynaphthalene. The nature of the unsubstituted ring should therefore affect the position of equilibrium attained and it was of interest to prepare a number of quinols with fused heterocyclic rings and examine their behaviour on fusion. The quinols (III), (IV), and (V; R = Me) were therefore prepared but unfortunately were not sufficiently stable to yield satisfactory results. No carbonyl compounds could be detected after heating of the dienols above the melting points for several minutes followed by rapid cooling, but as considerable decomposition occurred this is inconclusive. 4 : 7-Dihydroxythionaphthen and 5 : 8-dihydroxyquinoline were obtained from the corresponding quinones. Indole-*p*-quinones and quinols are new and are discussed below.



(I) (II) (III) (IV) (V) (VI)

Hydroxy- or methoxy-indoles have usually been prepared from suitably substituted *o*-nitrotoluenes (Blaikie and Perkin, *J.*, 1924, **125**, 307), 2 : β-dinitrostyrenes (Beer *et al.*, *J.*, 1948, 1605) or by the Fischer synthesis (Kermack, Perkin, and Robinson, *J.*, 1922, **121**, 1872). None of these methods is attractive for the synthesis of 4 : 7-dihydroxyindole (V; R = H) on account of the inaccessibility or instability of the required intermediates. 5 : 6-Dihydroxyindole has been obtained by oxidation of 3 : 4-dihydroxyphenylalanine (Harley-Mason and Bu'Lock, *J.*, 1951, 2248). The corresponding oxidation of 2 : 5-dihydroxyphenylalanine or 2-(2 : 5-dihydroxyphenyl)ethylamine seemed a possible route to 4 : 7-dihydroxyindole but after our preliminary experiments with the former had failed Cromartie and Harley-Mason (*J.*, 1952, 2525) showed that these oxidations took a different course and gave 5-hydroxyindole. Previously, with the intention of preparing the dihydroxyphenylethylamine from the corresponding β-nitrostyrene, we had attempted to condense 2 : 5-dihydroxybenzaldehyde with nitromethane. A variety of conditions were tried without success (cf. Remfry, *J.*, 1911, **99**, 282); when 2 : 5-diacetoxybenzaldehyde and piperidine as catalyst were used partial deacetylation occurred. The formation of indole and *N*-ethylindole by cyclisation of anilinoacetaldehyde diethyl acetal and its *N*-ethyl derivative has been claimed by Nencki and Berliner (G.P. 40,889) and by Räth (*Ber.*, 1924, **57**, 715) respectively. Although Janetsky, Verkade, and Meerburg (*Rec. Trav. chim.*, 1947, **66**, 317) were unable to repeat this work, an attempt to cyclise the more reactive 2 : 5-dimethoxyanilinoacetaldehyde diethyl acetal seemed worth while. However treatment of the latter under various acid conditions gave only amorphous solids from which no 4 : 7-dimethoxyindole could be isolated, in agreement with Janetsky *et al.*

* Parts I and II, *J.*, 1950, 1737; 1952, 2759.

Attention was then turned to more accessible alkylated 4 : 7-dihydroxyindoles. Reduction of the readily available 2 : 3-dimethyl-7-nitroindole (Schofield and Theobald, *J.*, 1949, 796) gave the amine which was coupled with diazotised sulphanilic acid in acid solution. Oxidation of the crude diamine, obtained by reduction of the azo-compound, with ferric chloride or acid dichromate gave red solutions but no quinone could be isolated. This general method for preparing quinones does not seem to be widely applicable to heterocyclic compounds. We experienced a similar failure in the oxidation of 4 : 7-diaminobenzothiadiazole (obtained as above), Fieser and Martin (*J. Amer. Chem. Soc.*, 1935, **57**, 1835) were unable to isolate a quinone after oxidation of 4-amino-7-hydroxybenzotriazole, and the oxidation of 5-amino-8-hydroxy*iso*quinoline is also anomalous (*idem*, *ibid.*, p. 1840).

A method of preparing 4 : 7-dihydroxyindoles was ultimately found in the Bischler synthesis. Condensation of 2 : 5-dimethoxyaniline with 1-bromoethyl methyl ketone gave 4 : 7-dimethoxy-2 : 3-dimethylindole from which the quinol (V; R = Me) was obtained by demethylation with aluminium chloride. The quinone was also prepared. 1 : 2 : 3 : 4-Tetrahydro-5 : 8-dimethoxycarbazole, and the corresponding quinol (VI) and quinone, were similarly obtained from 2 : 5-dimethoxyaniline and 2-chloro*cyclo*hexanone. The dimethyl ether was smoothly dehydrogenated with chloranil (Barclay and Campbell, *J.*, 1945, 530) to 1 : 4-dimethoxycarbazole but we were unable to demethylate this product. Attempts to dehydrogenate (VI) and the tetrahydrocarbazolequinone were also unsuccessful.

Experimental

7-Amino-2 : 3-dimethylindole.—(*a*) Sodium dithionite (2 g.) was added to a suspension of 2 : 3-dimethyl-7-nitroindole (0·57 g.) in a boiling mixture of alcohol (25 c.c.), water (40 c.c.), and sodium hydroxide (5 c.c., 2N). After 5 min. more dithionite (2 g.) was added and refluxing continued until an almost colourless solution was obtained (30 min.). This was diluted with water (50 c.c.) and extracted with ether. Evaporation of the dried extract yielded a solid which crystallised from water to give the amine as whitish-grey needles, m. p. 126° (decomp.) (40%). Recrystallisation was carried out rapidly as the amine decomposes at high temperatures. (*b*) 2 : 3-Dimethyl-7-nitroindole (0·48 g.) in 50% ethyl acetate–ethanol (20 c.c.) was hydrogenated in the presence of Raney nickel and the *amine* isolated by evaporation to dryness. It recrystallised from water in whitish-grey needles, m. p. 126° (decomp.) (45%) identical with those obtained as in (*a*) (Found: C, 75·2; H, 7·5; N, 17·5. $C_{10}H_{12}N_2$ requires C, 75·0; H, 7·5; N, 17·5%).

2 : 5-Dimethoxynitrobenzene.—The method described by Ungnade and Zilch (*J. Org. Chem.*, 1951, **16**, 64) gave dinitration products. The following procedure was found convenient: to a solution of 1 : 4-dimethoxybenzene (10 g.) in glacial acetic acid (40 c.c.) was added slowly with stirring a mixture of concentrated nitric acid (10 c.c.) and water (10 c.c.), the temperature being maintained below 40°. The yellow nitro-compound separated during the addition and was collected after dilution of the mixture with water (50 c.c.). Crystallisation from methanol yielded yellow needles, m. p. 72° (91%).

2 : 5-Dimethoxyaniline.—2 : 5-Dimethoxynitrobenzene (18·3 g.) in ethyl acetate (100 c.c.) was shaken with hydrogen and 5% palladised strontium carbonate until hydrogen uptake ceased (80 min.). The amine was obtained by evaporation to dryness and had m. p. 80° (98%).

2 : 5-Dimethoxyanilinoacetaldehyde Diethyl Acetal.—A mixture of 2 : 5-dimethoxyaniline (15·3 g.) and bromoacetal (19·9 g.) was refluxed in 95% ethanol (50 c.c.) in the presence of anhydrous sodium hydrogen carbonate (12·6 g.) for 48 hr. The solvent was then removed by evaporation on a water-bath and water added to the residue; an oil was precipitated. This was isolated with ether, dried ($MgSO_4$), and fractionated under reduced pressure to give (1) unchanged bromoacetal, b. p. 61—62°/10—11 mm., and (2) 2 : 5-dimethoxyaniline, b. p. 151°/10—11 mm. The latter solidified and was recrystallised from light petroleum (22% recovery). The high-boiling residue was distilled at 141°/1 mm., to give the required *acetal* as a colourless liquid (68%) (Found: C, 62·5; H, 8·65. $C_{14}H_{23}O_4N$ requires C, 62·45; H, 8·6%).

4 : 7-Dimethoxy-2 : 3-dimethylindole.—A mixture of 2 : 5-dimethoxyaniline (7·6 g.) and 1-bromoethyl methyl ketone (3·8 g.) was set aside overnight. The reddish-brown mixture was then heated in an oil-bath at 125° for 30 min., cooled, and brought to the boil with hydro-

chloric acid (35 c.c., 2N). After being chilled, the acid solution was decanted from a black tar. The tar was extracted with boiling ether (2 × 100 c.c.), and the extracts were dried and evaporated. Vacuum-distillation of the residual solid gave the *indole* as a brown liquid, b. p. *ca.* 135—140°/1—2 mm., which solidified. One recrystallisation from aqueous alcohol (charcoal) afforded plates, m. p. 103—104° (61%) (Found: C, 70·3; H, 7·4; N, 6·9. $C_{12}H_{15}O_2N$ requires C, 70·2; H, 7·35; N, 6·8%). The *picrate* formed dark brown needles, m. p. 167° (from ethanol) (Found: C, 49·9; H, 3·9; N, 12·6. $C_{18}H_{18}O_9N_4$ requires C, 49·8; H, 4·15; N, 12·9%).

4 : 7-*Dihydroxy*-2 : 3-*dimethylindole*.—4 : 7-Dimethoxy-2 : 3-dimethylindole (1·8 g.) was refluxed in dry benzene (60 c.c.) with powdered anhydrous aluminium chloride (12·6 g.) for 12 hr. After cooling in ice the solid mass was broken up and treated with ice and hydrochloric acid. The product was collected and crystallised from benzene and then from water (containing a little sodium dithionite). The *quinol* separated as feathery crystals, m. p. 205—206° (decomp.) (bath preheated to 200°) (54%) (Found: C, 67·7; H, 5·95; N, 7·8. $C_{10}H_{11}O_2N$ requires C, 67·75; H, 6·2; N, 7·92%). The *diacetate* had m. p. 138° (from light petroleum) (Found: C, 64·2; H, 5·75; N, 5·5. $C_{14}H_{15}O_4N$ requires C, 63·9; H, 5·8; N, 5·35%).

2 : 3-*Dimethylindole*-4 : 7-*quinone*.—The above quinol (0·2 g.) was dissolved in acetone (20 c.c.) and water (10 c.c.) and treated with a solution of potassium dichromate (0·5 g.) in water (3 c.c.) containing concentrated sulphuric acid (0·5 c.c.). After 30 min. the red solution was diluted with water (30 c.c.) and extracted with ether. Evaporation of the dried ($MgSO_4$) extracts afforded a red solid. Recrystallisation from benzene yielded the *quinone* in red leaflets, m. p. 215—217° (decomp.) (79%) (Found: C, 68·35; H, 5·4; N, 8·0. $C_{10}H_9O_2N$ requires C, 68·55; H, 5·2; N, 8·0%).

1 : 2 : 3 : 4-*Tetrahydro*-5 : 8-*dimethoxycarbazole*.—2 : 5-Dimethoxyaniline (10 g.), 2-chloro-*cyclo*hexanone (5 g.), and ethanol (30 c.c.) were refluxed for 14 hr. The amine hydrochloride gradually separated and was collected, after chilling of the mixture in ice, and was washed with ether. The combined filtrate and washings were evaporated to dryness and the semi-solid residue was extracted twice with boiling ether. The extract was washed with 2N-hydrochloric acid, water, aqueous sodium carbonate, and dried and evaporated. The residual sticky solid distilled at 150°/1 mm., to give a yellow oil which solidified. One recrystallisation from light petroleum (b. p. 80—90°) afforded the *tetrahydrocarbazole* in rosettes, m. p. 96° (52%) (Found: C, 72·5; H, 7·4; N, 6·15. $C_{14}H_{17}O_2N$ requires C, 72·7; H, 7·4; N, 6·1%). The *picrate* crystallised from ethanol in dark grey crystals, m. p. 153° (Found: C, 52·2; H, 4·25. $C_{20}H_{20}O_9N_4$ requires C, 52·2; H, 4·35%).

1 : 2 : 3 : 4-*Tetrahydro*-5 : 8-*dihydroxycarbazole*.—1 : 2 : 3 : 4-Tetrahydro-5 : 8-dimethoxycarbazole (0·5 g.) was refluxed in dry benzene (15 c.c.) with powdered anhydrous aluminium chloride (3·05 g.) for 12 hr. After decomposition with ice and hydrochloric acid the suspension obtained was extracted with ethyl acetate. Evaporation of the dried extract gave a brown solid which was crystallised first from benzene and then from aqueous alcohol (containing a little sodium dithionite). The *quinol* formed almost colourless needles, m. p. 225° (decomp.) (bath preheated to 205°) (48%) (Found: C, 70·6; H, 6·5; N, 6·8. $C_{12}H_{13}O_2N$ requires C, 70·9; H, 6·45; N, 6·9%). The *diacetate* had m. p. 152° (from light petroleum) (Found: C, 67·1; H, 5·85; N, 4·8. $C_{16}H_{17}O_4N$ requires C, 66·85; H, 5·95; N, 4·9%).

1 : 2 : 3 : 4-*Tetrahydrocarbazole*-5 : 8-*quinone*.—The above quinol (0·2 g.) in a mixture of acetone (25 c.c.) and water (10 c.c.) was oxidised by addition of potassium dichromate (0·75 g.) in water (3 c.c.) containing concentrated sulphuric acid (1 c.c.). After 30 min. the red solution was diluted with water and extracted with ether. The extract yielded a dark red solid which was crystallised from benzene. The *quinone* separated in red rosettes, m. p. 208—210° (decomp.) (68%) (Found: C, 71·55; H, 5·8; N, 6·8. $C_{12}H_{11}O_2N$ requires C, 71·6; H, 5·5; N, 6·95%).

1 : 4-*Dimethoxycarbazole*.—A mixture of 1 : 2 : 3 : 4-tetrahydro-5 : 8-dimethoxycarbazole (5·25 g.), chloranil (11·1 g.), and sulphur-free xylene (112 c.c.) was refluxed for 24 hr. After cooling, the tetrachloroquinol was filtered off and washed with ether, and the combined filtrate and washings were further diluted with ether, shaken with aqueous sodium hydroxide and then water, and dried. The solvent was evaporated and the residual dark blue oil distilled under reduced pressure, to give a faintly brown liquid, b. p. *ca.* 180—185°/1 mm., which solidified. Crystallisation from aqueous alcohol afforded small plates, m. p. 109—110° (72%). On a smaller scale the blue oil was conveniently purified by passing a benzene solution through a short column of alumina (Found: C, 74·2; H, 5·7; N, 6·5. $C_{14}H_{13}O_2N$ requires C, 74·0; H, 5·7; N, 6·2%). The carbazole gave a violet fluorescence in hydrocarbon solvents.

4 : 7-*Dihydroxythionaphthen*.—Thionaphthen-4 : 7-quinone (0·83 g.) in ethyl acetate

(20 c.c.) was reduced with hydrogen and Adams catalyst. The *quinol* was isolated by evaporation to small bulk and precipitation with light petroleum. It crystallised from benzene in felted needles, m. p. 171—172° (decomp.) (83%) (Found: C, 57·8; H, 3·2; S, 19·0. $C_8H_6O_2S$ requires C, 57·8; H, 3·6; S, 19·3%). The *diacetate* formed plates, m. p. 147° (from light petroleum) (Found: C, 57·6; H, 4·0; S, 12·6. $C_{12}H_{10}O_4S$ requires C, 57·6; H, 4·0; S, 12·8%).

5 : 8-*Dihydroxyquinoline*.—Quinoline-5 : 8-quinone (2·8 g.) in ethyl acetate (100 c.c.) was hydrogenated in presence of 5% palladised barium sulphate. The quinol separated from benzene in needles, m. p. 180° (68%).

5-*Acetoxy*-2-*hydroxybenzaldehyde*.—Piperidine (10 small drops) was added to 2 : 5-diacetoxybenzaldehyde (1 g.) in ethanol (20 c.c.) containing nitromethane (0·4 g.). After 24 hr. the mixture was poured into water; the precipitate crystallised from light petroleum (b. p. 50—60°) in needles, m. p. 77—77·5° (62%) (Found: C, 59·9; H, 4·6. Calc. for $C_9H_8O_4$ C, 60·0; H, 4·5%). The same compound was obtained when the experiment was repeated in the absence of nitromethane.

2 : 3-*Diacetoxynaphthalene* crystallises from aqueous alcohol in blades, m. p. 106° (Found: C, 68·85; H, 4·9. $C_{14}H_{12}O_4$ requires C, 68·8; H, 4·95%).

One of us (A. B.) thanks the Department of Scientific and Industrial Research for a Maintenance Allowance.

THE UNIVERSITY, OLD ABERDEEN. [*Received, June 30th*, 1954.]

Preparation of Rhodanine Derivatives as Possible Anthelmintics.

By ALEXANDER MACKIE and ANAND L. MISRA.

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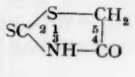
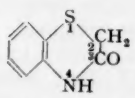
Rhodanine derivatives, including metallic derivatives of rhodanine, benzylidenerhodanines, compounds containing phenothiazine residues, and phenylimino-compounds have been prepared as possible anthelmintics. A mechanism for the formation of the phenylimino-compounds is suggested. Some of the benzylidene derivatives are very active towards liver fluke (*Fasciola hepatica*).

RHODANINE derivatives have been prepared with the view to testing of their anthelmintic activity *in vitro* against the roundworm *Ascaris lumbricoides* and liver fluke (*Fasciola hepatica*), since rhodanine (I) contains the group $-S{\cdot}CH_2{\cdot}CO{\cdot}NH-$, as does 2 : 3-dihydro-3-oxobenzo-1 : 4-thiazine (II), which was paralysant towards liver fluke (Mackie and Raeburn, *Brit. J. Pharmacol.*, 1952, **7**, 219).

(I) 

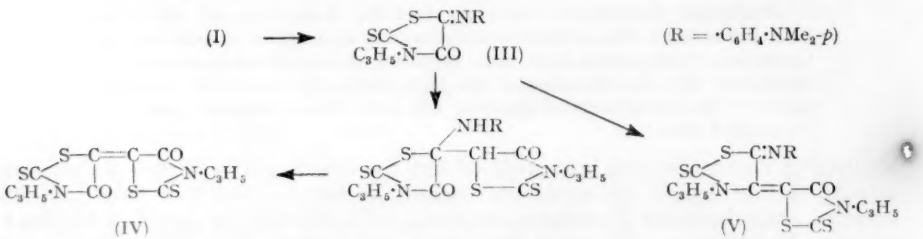
 (II)

Cupric, silver, and mercuric derivatives of rhodanine were prepared by precipitation methods (cf. Nencki, *J. pr. Chem.*, 1877, **16**, 4) and benzylidene derivatives by refluxing rhodanine with aldehydes and sodium acetate in glacial acetic acid (Campbell and McKail, *J.*, 1948, 1253). A number have already been reported, but were prepared by different methods, and in some cases the melting points quoted showed considerable differences. 2 : 4-Di-(2 : 4-dinitrophenyl)rhodanine was obtained in a similar manner from 2 : 4-dinitrochlorobenzene.

An attempt was made to obtain 5-benzylidene-2 : 4-dioxothiazolidine by hydrolysis, with 20% hydrochloric acid, of the bright orange-red 2-phenylhydrazone (A; m. p. 219°, sintering at 210°) from benzylidenerhodanine (Granacher, *Helv. Chim. Acta*, 1920, **3**, 152). A yellow compound (B) was isolated, which on recrystallisation from aqueous ethanol or glacial acetic acid, or on treatment with hot water, gave a dark red compound (C), m. p. 214° (no sintering; mixed m. p. with A showed no depression). Owing to the ready conversion into C, analytically pure B could not be prepared.

Infra-red spectra of A, B, and C revealed that A and C were identical, as were A, B, and C in chloroform solution. The substance B is possibly the unstable imide hydrochloride (presence of chlorine ions confirmed). The colour difference between A and C is almost certainly due to particle size.

When 3-allylrhodanine reacted with *p*-nitrosodimethylaniline in presence of fused sodium acetate and glacial acetic acid, the phenylimino-compound (III) was obtained in very small yield, together with 3:3′-diallyl-4:4′-dioxo-2:2′-dithio-5:5′-dithiazolidinylidene (IV). However, condensation in ethanol gave the asymmetric mono-*p*-dimethylaminophenylimino-compound (V). The mechanism of the condensation of *p*-nitrosodimethylaniline with compounds containing the ketomethylene group has previously been studied, *e.g.*, with β-coumaranone (Fries *et al.*, *Ber.*, 1910, **43**, 212; 1911, **44**, 114, 124) and thioindoxyl (Mann *et al.*, *J.*, 1942, 404; 1945, 893, 913). Mann found that the formation of thioindigo or thioindirubin from thioindoxyl depended on the medium and catalyst employed, strongly acidic media favouring the formation of thioindirubin, and weakly acidic, neutral, or basic media giving thioindigo. It appears that a similar mechanism applies to the condensations with 3-allylrhodanine as indicated in the annexed scheme. The structures of (III), (IV), and (V) were substantiated by their infra-red spectra, their CO frequencies being 1764, 1695, and 1709 cm.$^{-1}$ respectively. A five-membered cyclic lactam would be expected to absorb at about 1750 cm.$^{-1}$ if not conjugated, and at about 1710 cm.$^{-1}$ if αβ-unsaturated. The value for (IV) indicates that this is conjugated and has a *trans*-configuration. Both CO groups in (IV) were identical and the spectrum indicated a symmetrical structure, since no C:C frequency was exhibited. That all compounds contain the vinyl group is shown by the following wave-numbers: (III) 935, 985, 1420 cm.$^{-1}$; (IV) 925, 985, 1420 cm.$^{-1}$; (V) 990, 1385 cm.$^{-1}$; and *p*-substituted aromatic rings in (III) and (V) are indicated by the values 830—817 and 813 cm.$^{-1}$ respectively.



As phenothiazine is an anthelmintic, rhodanine and some of its derivatives were condensed with phenothiazine derivatives.

Unsuccessful attempts were made to condense rhodanine with γ-oxo-10-phenothiazinylbutyric acid (Winnick and Faith, U.S.P. 2,461,460/1949), according to the method of Allan, Maclean, and Newbold (*J.*, 1952, 5053).

3-Allyl-5-hydroxyiminorhodanine was prepared by the action of sodium nitrite on 3-allylrhodanine in aqueous acetic acid, with the view to obtaining the diketone and subsequently quinoxalines, but the hydroxyimino-compound could not be hydrolysed.

The biological tests will be published elsewhere; some of the benzylidene derivatives were very active towards liver fluke.

Experimental

A slight excess of aqueous copper sulphate, silver nitrate, and mercuric acetate was added severally to ethanolic solutions of rhodanine for the cupric and mercuric salts and to an aqueous ammoniacal solution of rhodanine for the silver salt. The precipitates were washed in turn with water and hot ethanol. Rhodanine (1·25 g.) gave a copper salt (2 g.), dark brown amorphous powder, m. p. 128—130° (decomp.) (Found: C, 21·5; H, 1·4. Calc. for $C_6H_4O_2N_2S_4Cu$: C, 21·9; H, 1·2%), a silver salt (2·5 g.), greenish-yellow amorphous powder, m. p. 230—232° (decomp.) (Found: C, 15·7; H, 1·2. Calc. for $C_3H_2ONS_2Ag$: C, 15·0; H,

0·8%), and a mercuric salt (2·2 g.), yellow amorphous powder, m. p. 240° (decomp.) (Found : C, 14·3; H, 0·9. Calc. for $C_6H_4O_2N_2S_4Hg,H_2O$: C, 14·7; H, 1·2%).

3-Allylrhodanine.—This was obtained (68%) by Andreasch and Zipser's method (*Monatsh.*, 1903, **24**, 499). It had b. p. 139°/6 mm., m. p. 48—49°. Andreasch and Zipser obtained a yellow oil.

Benzylidene Derivatives.—These were obtained by Campbell and McKail's method (*J.*, 1948, 1253), as follows : *o*-Nitrobenzylidenerhodanine, yellow needles (from glacial acetic acid) (83%), m. p. 188—190° (decomp.); Bondzynski (*Monatsh.*, 1887, **8**, 349) gives m. p. 188—190° (decomp.). Salicylidenerhodanine, yellow needles (from glacial acetic acid) (63%), m. p. 218—220° (decomp.); Zipser (*ibid.*, 1902, **23**, 958) gives m. p. 200° (decomp.); Bargellini (*Atti R. Accad. Lincei*, 1906, **15**, [i], 35) gives 218—219° (decomp.). *p*-Hydroxybenzylidenerhodanine, yellow needles (from aqueous pyridine) (75%), m. p. 258—260° (decomp.); Bargellini (*loc. cit.*) gives m. p. 260°. *p*-Anisylidenerhodanine, yellowish-brown needles (from glacial acetic acid) (77%), m. p. 250° (decomp.), sinters at 240° (Found : C, 53·3; H, 3·6. Calc. for $C_{11}H_9O_2NS_2$: C, 52·6; H, 3·6%); Andreasch and Zipser (*loc. cit.*) give m. p. 130—142° (decomp.). Cinnamylidenerhodanine, yellow needles (from xylene) (81%), m. p. 220—225° (decomp.); Andreasch and Zipser (*Monatsh.*, 1902, **23**, 958) give m. p. 208—211° (decomp.); Bargellini (*loc. cit.*) gives 220—221° (decomp.). *o*-Nitrocinnamylidenerhodanine, yellow needles (from aqueous pyridine) (72%), m. p. 248—250°; Brown, Bradsher, Bond, and Potter (*J. Amer. Chem. Soc.*, 1951, **73**, 2357) give m. p. 250°. Piperonylidenerhodanine, yellow needles (from aqueous pyridine) (48%), m. p. 255° (decomp.); Andreasch and Zipser (*loc. cit.*, 1903) give m. p. 245° (decomp.); Bargellini (*loc. cit.*) gives 256—258° (decomp.). *p*-Dimethylaminobenzylidenerhodanine, deep red needles (from xylene) (56%), m. p. 270° (decomp.); Andreasch and Zipser (*Monatsh.*, 1905, **26**, 1191) give m. p. 246° (decomp.); Bargellini (*Atti R. Accad. Lincei*, 1906, **15**, [i], 181) gives 270° (decomp.). Furfurylidenerhodanine, golden-yellow needles (from absolute ethanol) (87%), m. p. 229—231° (decomp.) (Found : C, 45·4; H, 2·6. Calc. for $C_8H_5O_2NS_2$: C, 45·4; H, 2·4%). Andreasch and Zipser record sintering at 204° only; Bargellini (*loc. cit.*, p. 35) gives m. p. 220° (decomp.). 3-Formyl-10-methylphenothiazine (Buu-Hoï and Hoán, *J.*, 1951, 1834) (4·25 g.) gave 5-(10-*methyl*-3-*phenothiazinylmethylene*)*rhodanine*, purified by recrystallisation from aqueous pyridine as dark red needles (5 g.), m. p. 247—248° (decomp.) (Found : C, 57·3; H, 3·8. $C_{17}H_{12}ON_2S_3$ requires C, 57·3; H, 3·4%). 3-*Allyl*-5-(10-*methyl*-3-*phenothazinylmethylene*)*rhodanine* was obtained similarly from 3-allylrhodanine as brick-red prisms (82%) (from aqueous acetone), m. p. 162—164° (Found : C, 60·5; H, 4·3. $C_{20}H_{16}ON_2S_3$ requires C, 60·6; H, 4·0%). 10-(5-*Benzylidene*-4-*oxo*-2-*thiazolinylthioacetyl*)*phenothazine* was prepared by adding to hot ethanolic benzylidenerhodanine (Andreasch and Zipser, *loc. cit.*) (2 g. in 125 c.c.) aqueous sodium acetate (4 g. in 5 c.c.), followed by boiling ethanolic 10-chloroacetylphenothiazine (Dahlbom and Ekstrand, *Acta Chem. Scand.*, 1951, **5**, 102) (3 g. in 10 c.c.). The reddish mixture was refluxed on the water-bath for 4 hr. and the product which separated recrystallised from glacial acetic acid as pale yellow needles (1·75 g.), m. p. 214—216° (decomp.) (Found : C, 62·1; H, 3·1. $C_{24}H_{16}O_2N_2S_3$ requires C, 62·6; H, 3·5%). The p-*chlorobenzylidene* analogue was similarly obtained from *p*-chlorobenzylidenerhodanine (McKail and Campbell, *J.*, 1948, 1253) (2·5 g.) and 10-chloroacetylphenothiazine (3 g.), forming pale yellow needles (2·5 g.), m. p. 213—214°, from glacial acetic acid (Found : C, 58·6; H, 3·3. $C_{24}H_{15}O_2N_2S_3Cl$ requires C, 58·2; H, 3·0%).

5-*Benzylidene*-4-*oxo*-2-*phenylhydrazonothiazolidine.*—This compound (A) was prepared by Granacher's method (*Helv. Chim. Acta*, 1920, **3**, 152). It recrystallised from xylene in bright orange-red plates, m. p. 219°, sintering at 210°. It (1·5 g.) was refluxed with 20% hydrochloric acid (100 c.c.) for 3 hr., the colour changing to pale yellow. The suspension was filtered. The residue was washed with cold water and ether and dried *in vacuo*. When this yellow compound (B) (1·5 g.) was heated at about 170°, or recrystallised from aqueous ethanol or glacial acetic acid, or treated with hot water, a dark red compound (C) was obtained, m. p. 214° (no sintering); the mixed m. p. with A showed no depression, but the m. p. of C was not raised by repeated recrystallisation.

4-(2 : 4-*Dinitrophenyl*)-2-(2 : 4-*dinitrophenylthio*)-4-*oxothiazolidine.*—Hot aqueous sodium acetate (3·5 g. in 5 c.c.) was added to a boiling absolute ethanolic solution of rhodanine (1 g. in 10 c.c.), then hot absolute ethanolic 2 : 4-dinitrochlorobenzene (3 g. in 10 c.c.). The mixture was refluxed for 2 hr. The *product* which separated recrystallised from aqueous acetone as yellow prisms (2 g.), m. p. 197—198° (Found : N, 15·5. $C_{15}H_7O_9N_5S_2$ requires N, 15·1%).

3-*Allyl*-5-p-*dimethylaminophenyliminorhodanine* (III).—3-Allylrhodanine (8·5 g.), *p*-nitrosodimethylaniline (7·5 g.), fused sodium acetate (10 g.), and glacial acetic acid (30 c.c.) were

refluxed for 4 hr. The *product* separated as a gum which crystallised from absolute ethanol as red needles (1 g.), m. p. 155—156°, sinter at 140° (Found: N, 13·3. $C_{14}H_{15}ON_3S_2$ requires N, 13·7%).

3 : 3′-*Diallyl*-4 : 4′-*dioxo*-2 : 2′-*dithio*-5 : 5′-*dithiazolylidene* (IV).—The gummy mass obtained as above was refluxed with benzene (charcoal). The *product* crystallised from benzene–ethanol as orange plates (1·5 g.), m. p. 184—186° (Found: C, 42·5; H, 2·7; N, 7·5. $C_{12}H_{10}O_2N_2S_4$ requires C, 42·1; H, 2·9; N, 8·1%).

3 : 3′-*Diallyl*-5-p-*dimethylaminophenylimino*-4′-*oxo*-2 : 2′-*dithio*-4 : 5′-*dithiazolidinylidene* (V).—The above condensation, carried out in ethanol instead of acetic acid, was complete in 0·5 hr. The *product* which separated recrystallised from acetic acid (charcoal) and then from alcohol as dark red needles (1·25 g. from 3·5 g.), m. p. 145—146° (Found: C, 51·9; H, 4·3; N, 12·9. $C_{20}H_{20}ON_4S_4$ requires C, 52·2; H, 4·3; N, 12·2%). Its red ethanolic solution changed to violet in presence of a trace of silver, being thus distinguished from (III) and (IV) which gave no colour.

3-*Allyl*-5-*hydroxyiminorhodanine*.—Aqueous sodium nitrite (6·5 g. in 15 c.c.) was added slowly to a warm suspension of 3-allylrhodanine (15 g.) in 2N-acetic acid (150 c.c.), and the mixture slightly warmed for 15 min. The yellow oil changed to reddish-orange. The supernatant liquid was decanted and on cooling deposited the *hydroxyimino*-compound. The oil was repeatedly extracted with boiling water and the supernatant liquid cooled as before. Recrystallisation from benzene afforded the pure compound as yellow plates (5 g.), m. p. 147—148° (Found: N, 13·6. $C_6H_6O_2N_2S_2$ requires N, 13·9%).

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The Hydrated Tetrafluorides of Uranium and Plutonium.

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The tetrafluorides of uranium and plutonium form two hydrates, the higher one having 2·5 molecules of water per metal atom and the lower one 2·0 molecules of water or less. Methods for their formation have been investigated.

The lower hydrate is pseudo-cubic, $a = 5{\cdot}69$ *kX* for the uranium and 5·63 *kX* for the plutonium compound, and the proposed structure is similar to that of uranium dioxide, the water molecules occupying vacant uranium sites and being hydrogen-bonded to the fluorine. Very little change of cell dimension was observed over the range $UF_4,2H_2O$ to $UF_4,0{\cdot}75H_2O$.

The fluorination, at temperatures below 100°, of the dioxides with gaseous hydrogen fluoride gives the lower fluoride hydrate and a second product which may be $M(OH)F_3,HF$.

A PREVIOUS communication described the preparation of anhydrous plutonium trifluoride and tetrafluoride by the reaction of gaseous hydrogen fluoride on plutonium dioxide at temperatures above 200° (Dawson, Elliott, Hurst, and Truswell, *J.*, 1954, 558). The same reactants at room temperature were found to give two new products, however, and the identification of these is given below.

During this investigation, it was shown that one of the products of the low-temperature fluorination was a hydrate of plutonium tetrafluoride, identical with a hydrate which could be precipitated from aqueous solution and isomorphous with a uranium tetrafluoride hydrate obtained by adding aqueous hydrofluoric acid to uranium tetrachloride solution. The uranium precipitation was then investigated in more detail, the products were analysed and their properties observed. *X*-Ray diffraction photographs showed that the uranium

fluoride hydrate could be indexed on the basis of a pseudo-cubic unit cell and it will be referred to below as the " pseudo-cubic hydrate."

Some of the experiments on the fluorination of uranium and plutonium dioxides gave an additional product with a more complex *X*-ray diffraction photograph. The analytical and *X*-ray data on this phase are given below and a possible formula is assigned; it will be referred to as " product A."

Several hydrates of uranium tetrafluoride have been reported. The highest hydrate definitely to be established is $UF_4,2{\cdot}5H_2O$; this was prepared by von Grosse by suspending ordinary precipitated uranium tetrafluoride in dilute aqueous hydrofluoric acid overnight (" The Chemistry of Uranium," Katz and Rabinowitch, National Nuclear Energy Series, VIII-5, McGraw-Hill Co. Inc., New York, 1951, p. 360). Khlopin and Gerling (*Zhur. Obschey Chim.*, 1936, **6**, 1701) and Khlopin and Yashenko (*Isvest. Akad. Nauk, U.S.S.R., Otdel. Khim. Nauk*, 1942, 87) claim to have isolated three hydrates, $UF_4,2H_2O$, $UF_4,1{\cdot}5H_2O$, and $UF_4,0{\cdot}5H_2O$, by electrolytic reduction of uranyl fluoride in aqueous hydrofluoric acid. Bolton (*Bull. Soc. chim.*, 1866, **2**, 450) found that addition of aqueous hydrofluoric acid to aqueous uranous chloride solution gave a precipitate which had the composition UF_4,H_2O after vacuum-drying or air-drying at 100°. It is now shown that the hydrates below the limit of $UF_4,2{\cdot}0H_2O$ all have the same structure.

Experimental

Analytical Procedures.—(a) *Uranium analysis.* A thermogravimetric curve for the air-ignition of a sample from precipitation No. 8 (Table 1) is shown in Fig. 1, curve *A*. It will be

Table 1. *Precipitation of uranous fluoride from hydrochloric acid solution by the addition of 40% aqueous hydrofluoric acid.*

No.	Temp.	Concentrations U (mg./ml.)	HCl (M)	Standing time	Final wash liquid	Found, % U	F	H_2O	Mole ratio H_2O/UF_4
1	20°	50	3·7	—	$COMe_2$	70·3	22·4	9·34	1·76
2	20	14	1·0	—	,,	69·6	—	9·85	1·87
3	20	7	0·52	—	,,	68·9	—	9·61	1·85
4	20	6	0·54	—	,,	69·0	—	9·96	1·91
5	20	5	0·37	—	,,	68·2	—	10·24	1·99
6	20	5	3·7	—	,,	68·8	—	9·45	1·82
7	20	4	0·30	—	,,	68·1	—	10·34	2·01
8	20	3·5	0·28	—	,,	68·2	21·8	10·67	2·06
9	20	2	0·15	—	,,	68·1	—	10·57	2·05
10	20	1·4	0·10	—	,,	68·1	—	10·84	2·10
11	20	1·25	0·09	—	,,	66·8	—	12·30	2·44
12	20	1·0	0·07	—	,,	66·95	—	12·08	2·38
13	20	0·70	0·05	30 Min.	,,	66·9	21·4	12·67	2·50
14	20	0·55	0·04	30 Min.	,,	67·0	—	13·15	2·59
15	20	0·28	0·02	2·5 Days	,,	66·9	—	12·87	2·52
16	20	0·14	0·01	No ppt. after 3 days					
17	20	0·5	3·0	No ppt. except with very large excess of HF					
18	11	20	1·4	—	$COMe_2$	69·1	—	8·37	1·60
19	6	20	1·4	—	EtOH	69·8	22·2	9·20	1·74
20	20	20	1·4	—	,,	69·8	22·1	9·27	1·76
21	20	20	1·4	2 Days	,,	70·1	—	9·46	1·79
22	80	80	4	—	,,	70·9	22·9	7·67	1·43
23	20	8·5	14	—	$COMe_2$	70·3	—	8·24	1·55
24	20	8·5	14	—	EtOH	69·6	—	7·89	1·50
25	20	8·5	0·4	—	,,	69·2	22·5	9·26	1·77

seen that constant weight was attained at temperatures above 800° and the product was found to be U_3O_8 by *X*-ray diffraction analysis. Part of the thermogravimetric curve on sample 4 (Table 2), *i.e.*, $UF_4,2{\cdot}5H_2O$, is shown in Fig. 1, curve *B*, and this likewise gave a constant weight of U_3O_8 above 800°. These facts were used as the basis for uranium analysis, other samples being heated to constant weight at about 850°. This was found to be not completely reliable when anhydrous uranium tetrafluoride was used, since some of the sample was oxidised only as far as UO_2F_2 unless the sample was in the form of a very thin layer. This could be overcome, if it was known to have occurred, by adding a drop of sulphuric acid to the residue and re-igniting it. The hydrates were more easily converted into U_3O_8 than was the anhydrous fluoride.

(b) *Plutonium analysis.* Thermogravimetric curves indicated that the product of the ignition of plutonium fluoride hydrates in air at 700° was plutonium dioxide and this was used as the basis for plutonium analysis.

(c) *Water analysis.* It was evident from the thermogravimetric curves that at 300° the product of heating the hydrates in air was mainly anhydrous uranium tetrafluoride and this was confirmed by *X*-ray diffraction photographs. For the actual analyses, in order to prevent partial oxidation, the samples were heated to 300° in nitrogen which had been dried by passing through a bead trap immersed in liquid oxygen. The heating time was reduced to a minimum : preliminary tests indicated that 20 min. was sufficient. As a check against excessive oxidation, a sample of $UF_4,1{\cdot}6H_2O$ was heated to 300° for 20 min; the residue was then shaken with oxygen-free water to dissolve uranyl fluoride. Analysis of the solution for uranyl ion indicated that the extent of oxidation had been 0·5%.

Some of the first analyses were made by passing the nitrogen over the heated sample and then through Karl Fischer reagent. Back-titration of the excess of reagent with methanol of known water content and correction for an apparatus blank gave the amount of water in the sample. Preliminary trials of the method gave an H_2O/Ca ratio of 1·97 in $CaSO_4,2H_2O$ and an H_2O/Ba ratio of 2·06 in $BaCl_2,2H_2O$. Since the result obtained from the titration was found to agree with the weight loss of the sample to within 0·1 mole of H_2O per mole of UF_4, subsequent analyses were made by using the weight-change measurement only.

FIG. 1. *Thermogravimetric curves for two uranium fluoride hydrates.*

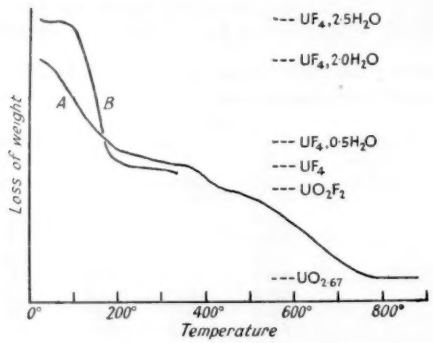
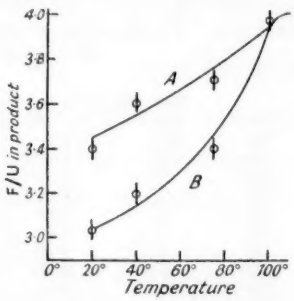


FIG. 2. *Fluorination of uranium dioxide with gaseous hydrogen fluoride and hydrogen: A, brown UO_3; B, black UO_2.*



Heating of plutonium fluoride hydrates in dry nitrogen to 300° produced the trifluoride. This is similar to the behaviour in a vacuum previously observed (Dawson *et al.*, *loc. cit.*) and is probably explained according to the equation

$$4PuF_4,nH_2O \longrightarrow 4PuF_3 + 4HF + O_2 + (4n - 2)H_2O$$

Consequently, a direct determination of the water content of the plutonium samples was not possible, and it was obtained by analogy with the uranium compounds and by difference after analysis for plutonium and fluorine.

(d) *Fluorine analysis.* The fluorine in the samples was estimated by the pyro-hydrolytic removal of hydrogen fluoride with steam at temperatures up to 1000°, condensation of the steam–hydrogen fluoride mixture, and titration with standard alkali. Duplicates agreed usually to $\pm 0{\cdot}5\%$ of the total fluorine content.

(e) X-*Ray diffraction analysis.* *X*-Ray diffraction photographs of the powdered specimens were taken, filtered copper-$K\alpha$ radiation and 11·4-cm. and 19-cm. Debye–Scherrer type cameras being used. Samples of the pseudo-cubic hydrates usually gave only low-angle lines, and the film lengths on the 11·4-cm. camera were calibrated by exposing silver-wire diffraction lines on the same films.

Uranium Fluoride System.—(a) *Precipitation of uranium tetrafluoride from aqueous solution.* A stock solution of quadrivalent uranium was made by dissolving uranium metal in concentrated hydrochloric acid and centrifuging off any precipitate which was formed. To obtain various concentrations the stock solution was diluted as indicated in Table 1. Precipitation of the fluoride hydrate was usually carried out in a plastic tube by the addition of about 10% calculated excess

of 40% aqueous hydrofluoric acid dropwise with stirring. The effects of some variations on this technique are noted in Table 1 and, except where a definite standing time is quoted, the precipitate was centrifuged off as soon as possible, washed once with water, sludged with water into a glass tube, and washed with acetone (a few samples were washed with absolute methanol, see Table 1). The samples were dried by being kept in laboratory air at room temperature.

(b) *Reactions of* UF_4 *and* UO_2 *with aqueous hydrofluoric acid.* Anhydrous uranium tetrafluoride and the dioxide both reacted slowly with aqueous hydrofluoric acid; if the dioxide was prepared by heating uranous oxalate in hydrogen at 350°, it reacted vigorously with the hydrofluoric acid. The results are summarised in Table 2. A sample from Expt. 4 gave the thermogravimetric curve shown in Fig. 1(*B*).

TABLE 2. *Reactions with aqueous hydrofluoric acid at* 20°.

	Reactant	HF concn. (% w/w)	Standing time (days)	Product (*X*-ray)	Analysis of product
1	UF_4	40	4	UF_4	75·1% U
2	UF_4	40	28	UF_4	—
3	UF_4	10	2·5	$UF_4,2·5H_2O$	—
4	UF_4	2	2	$UF_4,2·5H_2O$	66·6% U 12·4% H_2O 21·8% F
5	UO_2	40	6	UF_4,H_2O	69·8% U 8·4% H_2O
6	UO_2	10	2·5	$UF_4,2·5H_2O$	—
7	$UF_4,2·5H_2O$	10	2·5	$UF_4,2·5H_2O$	—
8	$UF_4,1·6H_2O$	10	2·5	$UF_4,2·5H_2O$	—
9	$UF_4,1·6H_2O$	2	2·5	$UF_4,2·5H_2O$	—

(c) *Fluorination of uranium dioxide by gaseous hydrogen fluoride.* This was investigated in order to determine whether the pseudo-cubic hydrate was formed at temperatures below 100°. This complex was, in fact, identified but was usually mixed with a second product still not characterised and called complex " A " below. The results are summarised in Fig. 2. The uranium dioxide obtained by heating uranous oxalate in hydrogen at 350° was sometimes brown and sometimes black (indicating excess of oxygen over the ideal composition UO_2). The products of hydrofluorination were dried in a high vacuum at room temperature before analysis. Trial experiments indicated a plateau (stable complex) on the thermogravimetric curve at 300°; heating fresh samples to this temperature to provide material for analysis gave the results shown in Table 3. The composition of the product with F/U = 3·0 is close to that of $U(OH)F_3$ [Calc.: U, 76·3; F, 18·3; (OH), 5·46%]. The products of fluorination at 75° evidently lose both hydrofluoric acid and water on heating. Complex " A " was converted into $UF_4,2·5H_2O$ by reaction with 10% aqueous hydrofluoric acid for three days.

TABLE 3.

	Original mixture				Complex formed at 300°			
Hydrofluorination conditions	U, %	F, %	(O + H), %	F/U	U, %	F, %	(O + H), %	F/U
From black UO_2 at 20°	74·5	18·1	7·4	3·04	75·6	18·7	5·7	3·0
,, brown UO_2 at 75°	70·8	20·9	8·3	3·7	76·3	19·2	4·5	3·1
,, black UO_2 at 75°	73·7	19·1	7·2	3·4	76·3	19·7	4·0	3·2

Plutonium Fluoride System.—(a) *Fluorination of* PuO_2 *with gaseous hydrogen fluoride at* 25°. Two products were obtained, isomorphous with the uranium compounds UF_4,H_2O and complex " A " described above. Usually the product was the pure pseudo-cubic compound in reactions performed on the 10—100-mg. scale, occasionally a mixture was obtained, and occasionally the complex " A " was the major phase (on the 1—10-mg. scale). Several quantitative fluorinations of plutonium dioxide were performed with gaseous hydrogen fluoride to produce the pure pseudo-cubic compound (according to the *X*-ray diffraction analysis) and the results are given in Table 4.

A fluorination of about 150 mg. of plutonium dioxide obtained by igniting the oxalate in air at 350° gave a vacuum-dried product with the pseudo-cubic *X*-ray pattern and having the analysis: Pu, 71·6; F, 23·2%; F : Pu, 4·07 : 1. A sample of this was used to obtain a thermogravimetric curve which showed that water was lost continuously as the temperature was raised to about 300°; above this temperature there was a gradual formation of plutonium dioxide.

Complex " A " was obtained by reaction of gaseous hydrogen fluoride with plutonium dioxide at temperatures between 20° and 100°, but the amounts obtained were insufficient for

TABLE 4.

	Starting material	Drying conditions	Wt. increase (%)	Product formula
1.	15·74 Mg. PuO_2 (350°) *	Vacuum, 20°	22·8	$PuF_4,1{\cdot}0H_2O$
2.	15·48 Mg. PuO_2 (350°)	Air, 105°	20·1	$PuF_4,0{\cdot}6H_2O$
3.	15·90 Mg. PuO_2 (660°)	Air, 105°	21·3	$PuF_4,0{\cdot}8H_2O$

* The number in parentheses indicates that the dioxide was obtained by ignition of the oxalate to that temperature.

analysis apart from *X*-ray diffraction photography. The same product was obtained irrespective of whether or not hydrogen was added to the hydrogen fluoride.

(b) *Precipitation from aqueous solution.* Stock solutions of quadrivalent plutonium in hydrochloric acid and nitric acid were found to contain negligible impurities by spectrographic analysis. After dilution of the solutions to the required concentrations (with 0·1M-acids), sufficient 40% aqueous hydrofluoric acid was added to make the solution about 10% in aqueous hydrofluoric acid and to precipitate the plutonium. The results are given in Table 5. After precipitation, the hydrate was centrifuged off, washed with acetone, and dried in air at room temperature. With the exception of sample 1, Table 5, the precipitations were done on the

TABLE 5.

	Plutonium, mg./ml.	Acid	Standing time	Product (*X*-ray)
1	18	HCl	30 min.	Pseudo-cubic hydrate
2	12	,,	15 ,,	,, ,,
3	3·2	,,	3 hr.	,, ,,
4	42	HNO_3	5 min.	Pseudo-cubic hydrate + additional phase
5	10	,,	1 hr.	Pseudo-cubic hydrate + additional phase
6	5	,,	16 hr.	$PuF_4,2{\cdot}5H_2O$
7	1·25	,,	,,	$PuF_4,2{\cdot}5H_2O$
8	0·5		3 days	No precipitate

1—10-mg. scale and a water-wash of the precipitates was omitted since the solubilities in the plutonium system were higher than in the uranium system. Sample 1 was prepared on a scale such that after a water-wash of the precipitate there was still sufficient for duplicate plutonium and fluorine analyses: Pu, 69·3; F, 21·5%; Pu : F, 1 : 3·9 (Calc. for $PuF_4,1{\cdot}6H_2O$: Pu, 69·5; F, 22·1%).

(c) *Reaction of* PuF_4 *and* PuO_2 *with aqueous hydrofluoric acid.* These experiments were performed at 20° on the 5-mg. scale in HF-resistant plastic tubes. After standing for 2 days in the aqueous hydrofluoric acid, the residues were washed with a small quantity of water, then with acetone, and were dried in air at room temperature. Both plutonium tetrafluoride and the dioxide reacted with 2, 10, and 40% aqueous hydrofluoric acid to give $PuF_4,2{\cdot}5H_2O$.

DISCUSSION

(a) *Chemical.*—The tetrafluorides of uranium and plutonium have two hydrates; the higher one, $MF_4,2{\cdot}5H_2O$, has been reported previously (von Grosse, *loc. cit.*; Zachariasen, reported in Katz and Rabinowitch, *op. cit.*, p. 367). The lower hydrate MF_4,nH_2O, where $0{\cdot}5 < n < 2$, shows a simple cubic pattern on the *X*-ray diffraction photographs (see below).

In colour, the pseudo-cubic hydrate of uranium tetrafluoride is a somewhat darker green than $UF_4,2{\cdot}5H_2O$ although sometimes bluish-green samples were obtained. This variable colour was also noted by Khlopin and Yashenko (*loc. cit.*), who indicated that the effect was one of particle size since the chemical composition of the two forms was identical. There is a similar slight variation of colour in the plutonium system: the pseudo-cubic hydrate is a somewhat darker brown than $PuF_4,2{\cdot}5H_2O$ (in tungsten light the plutonium hydrates are pale green).

The higher hydrate, $UF_4,2{\cdot}5H_2O$, is stable in a vacuum at 25° and in air up to 100°

(Fig. 1); above this temperature it rapidly loses water to form UF_4. The lower hydrates of uranium and plutonium tetrafluorides are much less stable, however; Fig. 1 shows that as soon as the temperature is raised above room temperature water is lost until the composition is $MF_4,0{\cdot}5H_2O$. The conversion of $MF_4,0{\cdot}5H_2O$ into MF_4 is considerably slower than the original loss of water to $MF_4,0{\cdot}5H_2O$.

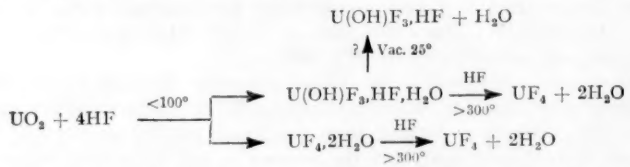
Some of the water is removed from the pseudo-cubic hydrate by shaking with dry methanol, whereas only adsorbed water appears to be removed from $UF_4,2{\cdot}5H_2O$. The higher hydrate, $UF_4,2{\cdot}5H_2O$, is formed from the lower one by suspending the latter in 2—10% aqueous hydrofluoric acid, but the process is not reversible; thus $UF_4,2{\cdot}5H_2O$ remained unchanged after standing in 40% aqueous hydrofluoric acid even though the latter produces the lower hydrate by reaction with uranium dioxide. The pseudo-cubic hydrate is probably only metastable. In the plutonium system, $MF_4,2{\cdot}5H_2O$ is more easily formed than in the uranium system.

During attempts to make hydrates of varying composition, the precipitation of uranous fluoride from aqueous hydrochloric acid was investigated in some detail. Table 1 shows that the temperature of the solution at the time of precipitation had no marked effect on the water content of the hydrate. The hydrochloric acid concentration had only a small effect on the water content (precipitations Nos. 5, 6, 24, 25). The largest effect was due to the concentration of the uranous ion: at concentrations less than 2 mg./ml. of U(IV) there was an increase of the water content of the precipitated hydrate from $UF_4,2{\cdot}0H_2O$ to $UF_4,2{\cdot}5H_2O$. A sample which was obtained intermediate between these values (precipitation No. 12; $UF_4,2{\cdot}38H_2O$) was shown by *X*-ray diffraction to be a mixture. This apparent concentration effect may include an effect due to the time of standing; at low uranium concentrations the precipitation rate was so low that it was necessary to leave some of the precipitate in the supernatant liquid much longer than for the higher uranium concentrations, and it was shown in other experiments (Table 2) that the lower hydrate is converted into the higher on contact with dilute aqueous hydrofluoric acid. It was shown by *X*-ray diffraction that precipitations from plutonium nitrate yielded a phase additional to the hydrates observed when using chloride solutions but this was not investigated in detail.

The hydrofluorination of plutonium dioxide below 100° gave two products. One was the pseudo-cubic PuF_4,H_2O, and the other had an *X*-ray diffraction pattern isomorphous with that of the uranium complex " A " obtained by hydrofluorination of uranium dioxide at room temperature. We failed to make the plutonium complex " A " phase on a scale greater than 10 mg. and so analytical data are not available. In the uranium system, however, fluorination of uranium dioxide prepared by heating the oxalate in hydrogen at 350° usually gave a mixture of product " A " and the pseudo-cubic phase with an average F/U ratio of less than 4. The *X*-ray diffraction patterns obtained from the vacuum-dried material were very poor, but both the pseudo-cubic and the complex " A " products were detected. Thermogravimetric curves indicated that heating the products in air to 300° gave a stable material after some loss of weight, and the F/U ratio became closer to 3·0. Also, at 300° some hydrogen fluoride was distilled off during the pyrohydrolytic determination of fluorine, whereas if the product had been previously heated to 300° in air no appreciable amount of fluorine was removed by pyrohydrolysis below 450°. This indicates that some of the fluorine in complex " A " is more loosely bound than the rest.

It seems probable that the hydrofluorination products are mixtures of UF_4,nH_2O and $U(OH)F_3,mHF$, where $0{\cdot}5 < n < 2$ and $m < 1$; because of the possible variability of m it is difficult to assess the relative amounts of the complexes in any particular product. At temperatures above about 300°, the product of the hydrofluorination is known to be anhydrous UF_4 which is produced according to the reaction $UO_2 + 4HF \longrightarrow UF_4 + 2H_2O$, the water being carried away in the hydrogen fluoride gas stream. Below 100°, however, the water produced in the reaction can be accommodated in the lattice structure of the product with the formation of the pseudo-cubic lower hydrate, this structure being very similar to that of the original uranium oxide (see below). Insufficient water is produced by the reaction for the formation of the more stable $UF_4,2{\cdot}5H_2O$. Both complex " A " and the pseudo-cubic hydrate are converted into anhydrous tetrafluoride in a stream of

hydrogen fluoride at elevated temperatures. Possibly, then, the hydrofluorination of UO_2 (or PuO_2) may follow either of the paths :



Finally, it is noteworthy that a complex, UF_4,HF, has been reported, although no *X*-ray data were quoted, from the reaction of UCl_4 with liquid anhydrous hydrogen fluoride (Kraus, quoted by Katz and Rabinowitch, *op. cit.*, p. 365). We have not, however, observed a F/U ratio greater than 4 on samples of the pseudo-cubic complex prepared by the methods described above. Presumably, there is not an easy exchange between H_2O and HF in the lattice once the complex has been formed. In the case of thorium, we observed a fluorine-to-metal ratio greater than 4 by heating ThF_4,H_2O in hydrogen fluoride at 400°.

(b) *Crystallographic.*—(i) UF_4,nH_2O. The diffraction patterns of samples in the composition range $UF_4,0{\cdot}75H_2O$ to $UF_4,2{\cdot}0H_2O$ were identical. The pattern could be indexed, from a consideration of the $\sin^2\theta$ values, as simple cubic with a cell edge $a = 2{\cdot}84\ kX$ and a volume $23\ kX^3$. This cell is too small to contain a molecular unit UF_4,nH_2O which has a calculated volume of $95\ kX^3$ on the basis of Zachariasen's values of 18—19 kX^3 for the volume of an oxygen or fluorine atom in a uranium fluoride (*Acta Cryst.*, 1951, **4**, 231).

If the unit cell is enlarged to $a\sqrt{2}$ with a volume of $64\ kX^3$, it is still too small to contain the UF_4,nH_2O. A further enlargement of the cell to $a\sqrt{3}$ is not possible, as the reflection with $\sin^2\theta = 0{\cdot}3654$ cannot be indexed. However, a unit cell of edge $2a$, giving a volume of $184\ kX^3$, will index the diffraction pattern and would also be compatible with two molecular units of UF_4,nH_2O per cell. The characteristic absences in the observed indices of the reflections are $h, k, l \neq 2n$.

Any distribution of the two uranium atoms on two-fold positions, irrespective of space-group, gave insufficient extinctions. So, similarly, did any distribution on one-fold positions.

A random distribution of the two U atoms over the 8 (*c*) special position of space-group $O_h^5 - Fm/m$ with the eight fluorine atoms on special positions 4 (*a*) and 4 (*b*) does give the requisite number of extinctions. The reflections with $h + k$, $k + l$, $l + h = 2n$, where $h, k, l = 2n + 1$, are necessarily absent even though permitted by the space-group because the U contribution to these phases is zero and the fluorine atoms on the 4 (*a*) position scatter completely out of phase with those on the 4 (*b*) position. Intensities calculated on this basis show good agreement with the observed intensities as can be seen from Table 6.

TABLE 6. $UF_4,1{\cdot}5H_2O$.

θ	$\sin^2\theta$	I_o	I_c *	*hkl*	θ	$\sin^2\theta$	I_o	I_c *	*hk*
15·71	0·0733	m	31	200	32·75	0·2927	w	15	400
22·49	0·1463	s	100	220	37·19	0·3654	w	15	420
27·93	0·2194	w	10	222	41·45	0·4382	w+	29	224

* $I_c \propto (1 + \cos^2 2\theta)F^2p/\sin^2\theta\cos\theta$.

It appears therefore that the observed data are compatible with UF_4,nH_2O, having a cubic structure with $a = 5{\cdot}69 \pm 0{\cdot}01\ kX$, space-group $O_h^5 - Fm3m$, with the two uranium atoms statistically distributed over the 8 (*c*) position and the eight fluorine atoms on the 4 (*a*) and 4 (*b*) positions. There would be two molecular units per unit cell, giving a co-ordination number of eight for the uranium. This suggested unit cell might well be a pseudo-cell, with the true cell being of lower symmetry. Attempts to index the pattern with a symmetry other than cubic failed, as did also attempts to detect lines which could be attributed to a " true " cell.

The water molecules in this structure would presumably be accommodated on the

8 (*c*) positions at points not occupied by the uranium atoms. Thus the unit cell could contain six water molecules, giving a formula $UF_4,3H_2O$.

On volume considerations, the number of molecules of water per unit cell would be unlikely to exceed four, *i.e.*, $UF_4,2H_2O$, and this is confirmed by the experimental evidence. Densities calculated on the basis $UF_4,2H_2O$ and UF_4,H_2O are respectively 6·32 and 5·98. For comparison, the densities of anhydrous UF_4 (Burbank, U.S. Atomic Energy Commission AECD 3216) and $UF_4,2{\cdot}5H_2O$ (Zachariasen, *loc. cit.*) are respectively 6·63 and 4·74.

The interatomic distances for the proposed structure can be calculated as 2·46 and 2·84 *kX* for U–F and F–F distances respectively, which are in fair agreement with the distances in other uranium fluorides. For example, in anhydrous UF_4 (Burbank, *loc. cit.*) the U–F and F–F distances are respectively 2·3 and 2·8 *kX*.

The O–F distance of 2·46 is rather small compared with the accepted radius sum of 2·76 for the oxide and fluoride ions. This seems to imply that this distance is really an O–H–F distance with the water hydrogen-bonded to the fluorine atoms.

TABLE 7.

n in UF_4,nH_2O	1·5	1·3	1·2	0·7
a, *kX*, ±0·01	5·69	5·67	5·67	5·65

Removal of part of the water, which would necessarily involve rupture of some O–H–F bonds, might be thought to cause some variation in cell volume. Some indication of cell shrinkage has been observed (Table 7) on removal of some of the water in these hydrates.

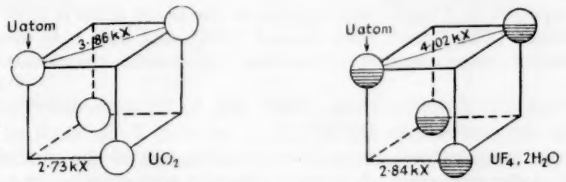


FIG. 3. *Comparison of the structures of* UO_2 *and* $UF_4,2H_2O$.

It is of interest to compare the proposed structure with that of UO_2 which is face-centred cubic. The oxygen atoms form a simple cubic array with a spacing of 2·73 *kX*, which is directly comparable to the simple cubic array of fluorine atoms with a spacing 2·84 *kX* in the proposed structure. The uranium atoms in UO_2 can be considered as being at four corners of a cube of spacing 2·73 *kX* with a closest-approach distance of 3·86 *kX*. In the case of the hydrate the two uranium atoms are randomly distributed over the eight corners of a cube of spacing 2·84 *kX*. However, as the closest-approach distance in this case is 4·02, one can consider 2 uranium atoms distributed over four corners of a cube similar to the arrangement in UO_2. The two structures are compared in Fig. 3. Apparently the structure of UF_4,nH_2O bears a closer resemblance to UO_2 than to either UF_4 (Burbank, *loc. cit.*) or $UF_4,2{\cdot}5H_2O$ (Zachariasen, *loc. cit.*).

(ii) PuF_4,nH_2O. Photographs of PuF_4,nH_2O, where $n < 2{\cdot}0$, were identical with those of UF_4,nH_2O. In the following Table the $\sin^2\theta$ values are given from which a cell constant $a = 5{\cdot}63 \pm 0{\cdot}01$ *kX* has been calculated. PuF_4,nH_2O thus appears to be isostructural with UF_4,nH_2O with a cubic cell slightly smaller owing to the difference in size of the heavy cations.

The calculated interatomic distances for Pu–F, F–F, and O–H–F have the values 2·43, 2·81, and 2·43 *kX*, respectively.

I_0	m	s	w	w	w	w	vvw *	vvw *	vvw *
$\sin^2\theta$	0·0742	0·1494	0·2251	0·3000	0·3747	0·4493	0·5976	0·6724	0·7478

* Lines are very diffuse.

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Thermochemistry of Organo-boron compounds. Part V. Ethoxychloroborines.*

By H. A. Skinner and N. B. Smith.

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Values are reported for the heats of hydrolysis of ethoxydichloroborine and diethoxychloroborine, from which the heats of formation ($\Delta Hf°$) in the liquid state are derived, *viz.*:

$$\Delta Hf°[B(OEt)Cl_2, \text{liq.}] = -158{\cdot}3 \pm 1{\cdot}2 \text{ kcal./mole}$$
$$\Delta Hf°[B(OEt)_2Cl, \text{liq.}] = -206{\cdot}3 \pm 1{\cdot}2 \text{ kcal./mole.}$$

The bond-energy term values of the B–Cl and B–OEt links in the group $B(OEt)_nCl_{3-n}$ ($n = 0, 1, 2, 3$), for which thermal data are now complete, are not constant throughout the group. The molecule $B(OEt)Cl_2$ is more stable by 4·8, and $B(OEt)_2Cl$ by 4·0 kcal./mole, than would be the case if the bonds should have the same energies as B–Cl in BCl_3 and as B–OEt in $B(OEt)_3$.

The enhancement in bond energy in the " mixed " molecules is attributed to variations in the extent of back-co-ordination in this group of molecules. The observed bond-energy variations—and the similar, but more marked, variations in the group $B(NMe_2)_nCl_{3-n}$ (cf. Part IV)—may be quantitatively reproduced by a molecular-orbital treatment of back-co-ordination, from which it appears that back-co-ordination to the boron atom is more effective from nitrogen (NMe_2) than from oxygen (OEt), and that both these atoms are appreciably more effective in this respect than is the chlorine atom.

Wiberg and Sütterlin (*Z. anorg. chem.*, 1931, **202**, 1, 22) have described the preparation and properties of the compounds $B(OEt)_nCl_{3-n}$ ($n = 1, 2, 3$), each of which is readily hydrolysed at room temperature, giving boric acid as one of the products. The heat of hydrolysis of one of these compounds (triethyl borate) was reported recently by Charnley, Skinner, and Smith (*J.*, 1952, 2288), and in this paper we deal with the heats of hydrolysis of the two remaining compounds of the group, diethoxychloroborine, $B(OEt)_2Cl$, and ethoxydichloroborine, $B(OEt)Cl_2$. The study follows closely the pattern of a previous study on the compounds $B(NMe_2)_nCl_{3-n}$, in which we observed that the bond-energy terms of the B–Cl and B–NMe_2 linkages are not additive throughout the group. The present results lead to a similar conclusion in respect of the B–Cl and B–OEt bond-energy terms in the group $B(OEt)_nCl_{3-n}$ ($n = 0, 1, 2, 3$).

Experimental

Preparation of Compounds.—Ethoxydichloroborine was prepared by slowly adding equivalent quantites of ethanol in dry pentane to boron trichloride in the same solvent, with efficient stirring and cooling. The bulk of the solvent was then removed by low-pressure distillation at −50°. The product was fractionated in an apparatus similar to that described by Wiberg and Sütterlin (*loc. cit.*), and the fraction, v. p. 26 mm. at 0°, was retained. This was stored at −78°. We have observed that ethoxydichloroborine deteriorates at room temperature, and decomposes rapidly at 60—70°.

Diethoxychloroborine was prepared by adding two equivalents of ethanol to one of boron trichloride, both in pentane. The solvent was removed at atmospheric pressure, and the product distilled under reduced pressure, through a 6″ gauze-packed column. The sample, b. p. 45·5—46°/60 mm., was retained.

Calorimeter.—The calorimeter has been previously described (Skinner and Smith, *Trans. Faraday Soc.*, 1953, **49**, 601). Hydrolysis was carried out by breaking thin glass ampoules, containing known weights of reactant, under the surface of water (500 g.) in the Dewar vessel. The temperature changes were followed through the change in resistance of a shielded thermistor element immersed in the solution. The experiments were carried out at 25°.

* Part IV, *J.*, 1954, 2324.

Units.—The calorimeter was calibrated electrically by the substitution method. Heat quantities are given in thermochemical calories, 1 calorie = 4·1840 abs. joule.

Results

Ethoxydichloroborine.—This compound reacts violently with water, and the reactant was diluted with carbon tetrachloride. The observed heats of hydrolysis, $\Delta H_{obs.}$, refer to the reaction :

$$B(OEt)Cl_2(liq./CCl_4) + (n + 3)H_2O(liq.) \longrightarrow (H_3BO_3 + 2HCl + EtOH),nH_2O \quad . \quad (1)$$

$\Delta H_{obs.}$ is related to the heat of formation of liquid * ethoxydichloroborine by the thermochemical equation :

$$\Delta Hf^\circ[B(OEt)Cl_2, liq.] = \Delta Hf^\circ\{H_3BO_3 + 2HCl + EtOH\},nH_2O - 3\Delta Hf^\circ(H_2O, liq.) - \Delta H_{obs.} \quad (2)$$

In using eqn. (2), thermal data from the following sources were accepted : $\Delta Hf^\circ(HCl,nH_2O)$ from " Selected Values of Chemical Thermodynamic Properties," Nat. Bur. Standards, Washington, Circular 500; $\Delta Hf^\circ(H_2O, liq.) = -68{\cdot}317$ kcal./mole (Circular 500); $\Delta Hf^\circ(EtOH,nH_2O) = -68{\cdot}706$ kcal./mole [from $\Delta Hf^\circ(EtOH, liq.) = -66{\cdot}356$, and the heat of solution ($-2{\cdot}35$ kcal./mole) measured by Bose (*Z. physikal. Chem.*, 1907, **58**, 585)†]; and

Table 1. *Heat of hydrolysis of* $B(OEt)Cl_2$.

Expt.	$B(OEt)Cl_2$ (mole)	n	$-\Delta H_{obs.}$ (kcal.)	$\Delta Hf^\circ[B(OEt)Cl_2]$ (kcal./mole)	Mean values (kcal./mole)
1	0·00736	3770	42·87	−158·1	
2	0·006165	4501	42·61	−158·4	$-\Delta H_{obs.} = 42{\cdot}5$
3	0·007214	3847	42·45	−158·5	$\Delta Hf^\circ = -158{\cdot}5$
4	0·004342	6391	42·00	−159·0	

$\Delta Hf^\circ(H_3BO_3,nH_2O) = -257{\cdot}33 \pm 0{\cdot}4$ kcal./mole (from Prosen, Johnson, and Pergiel, Nat. Bur. Standards, Report No. 1552, 1953). Table 1 contains a representative selection from our results. The mols. of reactant used in each experiment were determined by analysis of the Cl^- ion content of aliquot samples from the hydrolysed solution.

The possible error in $\Delta H_{obs.}$, after allowance for errors of analysis and of calorimetry, is estimated at *ca.* $\pm 0{\cdot}8$ kcal./mole.

Diethoxychloroborine.—Hydrolysis of this compound takes place sharply, but is less violent than that of ethoxydichloroborine, so that it was unnecessary to dilute the reactant for hydrolysis studies. According to Wiberg and Sütterlin (*loc. cit.*) diethoxychloroborine can be distilled without decomposition, and can be kept indefinitely. Our findings do not contradict these, but we noted slight contamination of the product by triethyl borate when it was prepared by the method described. Because of the similar volatilities of the two compounds, it is not easy to purify diethoxychloroborine completely. Our samples contained from 5 to 10% of triethyl borate, and correction on this account was necessary in the thermal studies.‡

The observed heats of hydrolysis, $\Delta H_{obs.}$, refer to the reaction :

$$B(OEt)_2Cl(liq.) + (n + 3)H_2O(liq.) \longrightarrow \{H_3BO_3 + HCl + 2EtOH\},nH_2O \quad . \quad . \quad . \quad (3)$$

and the ΔHf° values are derived from the equation :

$$\Delta Hf^\circ[B(OEt)_2Cl, liq.] = \Delta Hf^\circ\{H_3BO_3 + HCl + 2EtOH\},nH_2O - 3\Delta Hf^\circ(H_2O, liq.) - \Delta H_{obs.} \quad (4)$$

From nine experiments (in which n varied from 2200 to 3200), the mean $\Delta H_{obs.}$ was $-23{\cdot}5$ ($\pm 0{\cdot}3$) kcal./mole, and the mean value of ΔHf° was $-206{\cdot}3$ kcal./mole. Because of the unsatisfactory feature contained in the need for impurity corrections, we feel we ought to allot an error limit of $\pm 0{\cdot}7$ kcal./mole to $\Delta H_{obs.}$, although the observed spread was less than half this.

* The heat of mixing of $B(OEt)Cl_2$ (liq.) with CCl_4 (liq.) was assumed to be negligible.

† Circular 500 gives a slightly larger heat of solution; but we do not use it here since we made use of Bose's value in determining $\Delta Hf^\circ(Et_3BO_3)$.

‡ By using the heat of hydrolysis of ethyl borate measured by Charnley, Skinner, and Smith (*loc. cit.*). This correction was small, not more than 0·7 kcal./mole.

Discussion

In Table 2, we list the values obtained for the heats of formation of each member of the group $B(OEt)_nCl_{3-n}$, together with the latent heats of vaporisation, $\Delta H_{vap.}$, calculated from Wiberg and Sütterlin's vapour-pressure measurements (*loc. cit.*). The final column gives the heats of hydrolysis, $\Delta H_{hyd.}$, of the compounds in the gaseous state.

Table 2.

Compound	$\Delta Hf°$(liq.)	$\Delta H_{vap.}$	$\Delta Hf°$(gas)	$\Delta H_{hyd.}$
BCl_3	$-103{\cdot}0 \pm 1$	5·5	$-97{\cdot}5 \pm 1$	$-74{\cdot}7 \pm 0{\cdot}3$
$BCl_2{\cdot}OEt$	$-158{\cdot}3 \pm 1{\cdot}2$	$8{\cdot}4 \pm 0{\cdot}2$	$-149{\cdot}9 \pm 1{\cdot}4$	$-50{\cdot}9 \pm 1{\cdot}0$
$BCl(OEt)_2$	$-206{\cdot}3 \pm 1{\cdot}2$	$9{\cdot}3 \pm 0{\cdot}2$	$-197{\cdot}0 \pm 1{\cdot}4$	$-32{\cdot}8 \pm 0{\cdot}9$
$B(OEt)_3$	$-251{\cdot}3 \pm 1$	$10{\cdot}5 \pm 0{\cdot}2$	$-240{\cdot}8 \pm 1{\cdot}2$	$-17{\cdot}8 \pm 0{\cdot}3$

The variation in $\Delta H_{hyd.}$ from BCl_3 through the series to $B(OEt)_3$ is non-linear in relation to the number of chlorine atoms, from which it follows that the redistribution reactions between BCl_3 and $B(OEt)_3$ are not thermoneutral, and that the mean bond dissociation energies $\overline{D}$(B–Cl) and $\overline{D}$(B–OEt) are not constant in the group $B(OEt)_nCl_{3-n}$. From the values of $\Delta H_{hyd.}$ in Table 2 [or of ΔHf (gas)], we derive the heats of redistribution, ΔH_r, of the two redistribution reactions (5) and (6):

$$\tfrac{2}{3}BCl_3(g.) + \tfrac{1}{3}B(OEt)_3(g.) \longrightarrow BCl_2OEt(g.). \quad \Delta H_r = -4{\cdot}8\ (\pm 0{\cdot}7)\ \text{kcal./mole} \quad . \quad (5)$$

$$\tfrac{1}{3}BCl_3(g.) + \tfrac{2}{3}B(OEt)_3(g.) \longrightarrow BCl(OEt)_2(g.). \quad \Delta H_r = -4{\cdot}0\ (\pm 0{\cdot}7)\ \text{kcal./mole} \quad . \quad (6)$$

These ΔH_r are smaller (by a factor >2) than the heats of redistribution of the corresponding reactions between BCl_3 and $B(NMe_2)_3$ (cf. Part IV).

We propose to discuss the present results in essentially similar manner to our earlier discussion in Part IV, *i.e.*, in terms of π-conjugation (" back-co-ordination "). The conjugation problem is regarded as one of six electrons, extending over the central B atom and the three atoms trigonally attached to it. The localized reference system is considered to have the $2p_z$ boron orbital vacant, and to have p_z^2 pairs localized on each oxygen and/or chlorine atom. We need to estimate the energy stabilization arising from delocalization of these three p_z^2 pairs. The procedure may be illustrated by the example of $BCl_2{\cdot}OEt$, for which the secular equation is:

$$\begin{vmatrix} \alpha_B - \varepsilon & \gamma^* - S^*\varepsilon & \gamma - S\varepsilon & \gamma - S\varepsilon \\ \gamma^* - S^*\varepsilon & \alpha - \varepsilon_O & 0 & 0 \\ \gamma - S\varepsilon & 0 & \alpha_{Cl} - \varepsilon & 0 \\ \gamma - S\varepsilon & 0 & 0 & \alpha_{Cl} - \varepsilon \end{vmatrix} = 0 \quad . \quad . \quad . \quad (7)$$

In eqn. (7), α_B, α_O, and α_{Cl} are coulomb integrals, $\gamma^* = \gamma^*$(B–O) and $\gamma = \gamma$(B–Cl) are exchange integrals, and $S^* = S$(B–O) and $S = S$(B–Cl) are overlap integrals. The total π-electronic energy of the delocalized system is obtained by filling the three lowest-energy levels obtained on solution of (7). The energy stabilization (relative to the defined localized system) is symbolized $R_\pi(BOCl_2)$ and given by $2\left[\sum_{i=1}^{3}\varepsilon_i - 2\alpha_{Cl} - \alpha_O\right]$.

To assist the solution of (7) (and the similar equations relating to the systems BO_3, BO_2Cl, BCl_3), we have made the following substitutions:

$$\gamma - \frac{S}{2}(\alpha_O + \alpha_{Cl}) = \beta \qquad \gamma^* - \frac{S^*}{2}(\alpha_O + \alpha_{Cl}) = \beta^*$$

$$\beta = n\beta^*$$

$$(\alpha_{Cl} - \alpha_B) = m\beta^* \qquad (\alpha_O - \alpha_B) = 1{\cdot}5\,m\beta^*$$

$$S = 0{\cdot}206 \qquad S^* = 0{\cdot}189$$

The overlap integrals were calculated from the formulæ of Mulliken, Ricke, Orloff, and Orloff (*J. Chem. Phys.*, **1949**, **17**, 1248), the bond distances $r_{B-Cl} = 1{\cdot}73$ Å and $r_{B-O} = 1{\cdot}38$ Å being used. The assumption $(\alpha_O - \alpha_B) = 1{\cdot}5(\alpha_{Cl} - \alpha_B)$ is made to comply with the relative electronegativities of O, Cl, and B (Pauling's scale gives O = 3·5, Cl = 3·0, B = 2·0). Calculated R_π values (in units of β^*) for a range of values of the unknown parameters m and n are given in Table 3. The solutions of the secular equations relating to the systems

$BOCl_2$ and BO_2Cl were obtained for us by Dr. F. H. Sumner, using the Manchester University electronic computing machine.

TABLE 3. *R_π values in units of* β^*.

	n =	1·5	1·3	0·7	0·5	0·4	0·3
$m = 0·5$	$R_\pi(BCl_3)$	3·5498	3·0426	1·5305	1·0355	0·7926	0·5559
	$R_\pi(BOCl_2)$	3·1536	2·7549	1·7210	1·4473	1·3362	1·2465
	$R_\pi(BO_2Cl)$	2·6752	2·4383	1·8962	1·7802	1·7383	1·7086
	$R_\pi(BO_3)$	2·0599	2·0599	2·0599	2·0599	2·0599	2·0599
$m = 1·0$	$R_\pi(BCl_3)$	3·3109	2·8120	1·3466	0·8830	0·6622	0·4541
	$R_\pi(BOCl_2)$	2·8729	2·4885	1·4482	1·1699	1·0529	0·9551
	$R_\pi(BO_2Cl)$	2·3204	2·1021	1·5473	1·4210	1·3729	1·3329
	$R_\pi(BO_3)$	1·6434	1·6464	1·6434	1·6434	1·6434	1·6434
$m = 1·5$	$R_\pi(BCl_3)$	3·1064	2·6192	1·2136	0·7824	0·5830	0·3989
	$R_\pi(BOCl_2)$	2·6393	2·2630	1·2507	0·9800	0·8650	0·7769
	$R_\pi(BO_2Cl)$	2·0699	1·8445	1·2896	1·1616	1·1113	1·0712
	$R_\pi(BO_3)$	1·3291	1·3291	1·3291	1·3291	1·3291	1·3291

Table 4 gives values of two quantities, Δ_1 and Δ_2, defined by :

$$\Delta_1 = R_\pi(BOCl_2) - \tfrac{2}{3}R_\pi(BCl_3) - \tfrac{1}{3}R_\pi(BO_3) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8a)$$

$$\Delta_2 = R_\pi(BO_2Cl) - \tfrac{1}{3}R_\pi(BCl_3) - \tfrac{2}{3}R_\pi(BO_3) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8b)$$

TABLE 4. *Δ values in units of* β^*.

	n = 1·5	1·3	0·5	0·4	0·3
$m = 0·5$ Δ_1	0·1004	0·0398	0·0703	0·1211	0·1892
Δ_2	0·1186	0·0508	0·0617	0·1008	0·1500
$m = 1·0$ Δ_1	0·1179	0·0660	0·0335	0·0636	0·1046
Δ_2	0·1212	0·0692	0·0311	0·0566	0·0860
$m = 1·5$ Δ_1	0·1253	0·0738	0·0153	0·0334	0·0679
Δ_2	0·1480	0·0854	0·0147	0·0309	0·0522

Our suggestion is that the ΔH_r of eqns. (5) and (6) are to be identified with Δ_1 and Δ_2 respectively.

The negative ΔH_r of eqns. (5) and (6) imply that there is an *enhancement* of the bond-energy term values (of B–Cl, or B–OEt, or both) in the " mixed " molecules relative to their values in the " parent " molecules, BCl_3 and $B(OEt)_3$. Experimentally, the enhancement is found to be larger, by 0·8 kcal., in the $BOCl_2$ system (eqn. 5) than in the BO_2Cl system (eqn. 6). But the limits of error attached to the ΔH_r values are too large to allow us to say definitely that ΔH_r of eqn. (5) is more negative than ΔH_r of eqn. (6), and therefore that numerically, $|\Delta_1| > |\Delta_2|$. The presumption in this direction is, however, strengthened by our studies on the dimethylaminochloroborines, in which we found the enhancement to be larger in the $BNCl_2$ system than in BN_2Cl, and concluded that the corresponding Δ values follow $|\Delta_1| > |\Delta_2|$.

The calculated Δ values predict enhancement in the mixed molecules for a range of values of n greater or less than unity, but whereas for $n > 1$, $|\Delta_2| > |\Delta_1|$, for $n < 1$, $|\Delta_1| > |\Delta_2|$. For the remainder of this discussion, we accept (with due reservation) the strong presumption from experiment that the proper interpretation is $|\Delta_1| > |\Delta_2|$, and $n < 1$.

In the discussion of Part IV, we remarked that the Δ_1 and Δ_2 there reported are very satisfactorily reproduced by a particular choice of parameter values (*i.e.*, n, m), leading to $\beta^*(B–N) = -43·5$ kcal., $(\alpha_{Cl}–\alpha_B) = -21·75$ kcal., and $R_\pi(BCl_3) = -21·6$ kcal. It is useful, for comparison of the present study with the earlier one, to adopt fixed reference points (common to both) so that we retain for the moment the values for $(\alpha_{Cl}–\alpha_B)$ and $R_\pi(BCl_3)$ given above. With these restrictions, the parameter values leading to agreement with our present results are quite sharply defined, as may be seen from the calculated Δ values below :

n	m	β^*(B–O)	Δ_1 (calc.)	Δ_2 (calc.)
0·30	0·54	−40·1	−7·2	−5·7
0·33	0·60	−36·2	−5·3	−4·3
0·34	0·62	−35·1	−4·7	−3·9
0·35	0·64	−34·1	−4·2	−3·6
0·40	0·72	−30·1	−2·75	−2·35

Good agreement with the observed $\Delta_1 = -4{\cdot}8$, $\Delta_2 = -4{\cdot}0$, is given by $\beta^*(\text{B–O}) = -35{\cdot}1 \pm 1$ kcal. The important point is that the ratio $\beta^*(\text{B–N}) : \beta^*(\text{B–O})$ is found to greater than unity.

However, the choice $\beta^*(\text{B–N}) = -43{\cdot}5$ kcal. does not represent a unique solution to the problem discussed in Part IV, and a range of parameter values can be chosen to give agreement (within the limits of experimental error) with the observed Δ values. For example, the choice of parameters leading to $\beta^*(\text{B–N}) = -48$ kcal. and $(\alpha_{\text{Cl}}-\alpha_{\text{B}}) = -36$ kcal. is only slightly inferior to the one we have already used. If we now adopt $(\alpha_{\text{Cl}}-\alpha_{\text{B}}) = -36$ kcal. and $R_\pi(\text{BCl}_3) = -14{\cdot}8$ kcal. [determined by the value of $\beta^*(\text{B–N})$] as fixed points in the present problem, we obtain the Δ values :

n	m	β^*(B–O)	Δ_1 (calc.)	Δ_2 (calc.)
0·25	0·90	−40·0	−5·6	−4·6
0·305	1·10	−32·7	−3·3	−2·6

from which it is clear that good agreement with experimental observation requires $\beta^*(\text{B–O})$ to be *less* negative than $\beta^*(\text{B–N}) = -48$ kcal., so that, again, the condition $\beta^*(\text{B–N})/\beta^*(\text{B–O}) > 1$ is found to hold.

From the equations defining the β^* (and relating them to the exchange integrals γ^*) it follows that :

$$\frac{\gamma^*(\text{B–N})}{\gamma^*(\text{B–O})} = \frac{\beta^*(\text{B–N}) + 0{\cdot}22\alpha_{\text{Cl}}}{\beta^*(\text{B–O})\{1 + 0{\cdot}04715m\} + 0{\cdot}189\alpha_{\text{Cl}}} \quad \ldots\ldots (9)$$

and, since m is most unlikely to be a large number, and both the β^* and α_{Cl} are negative quantities, the condition $\beta^*(\text{B–N})/\beta^*(\text{B–O}) > 1$ leads to the more significant conclusion that the ratio $\gamma^*(\text{B–N})/\gamma^*(\text{B–O})$ is also larger than unity. Furthermore, the acceptable values of the parameter n (all of which are fractional) leave no doubt that $\beta^*(\text{B–O})/\beta(\text{B–Cl}) > 1$, and that $\gamma^*(\text{B–O})/\gamma(\text{B–Cl}) > 1$. The implications are that the N atom back-co-ordinates more powerfully to B than does the O atom, and that both N and O are appreciably more effective in this respect than is the Cl atom.

This order of effectiveness ($\text{N} > \text{O} \gg \text{Cl}$) in back-co-ordination to B is reflected in the strengths of the *co-ordinate* links formed by trimethylamine and diethyl ether with boron trifluoride [$D(\text{Me}_3\text{N}\rightarrow\text{BF}_3) \sim 28$ kcal./mole, $D(\text{EtO}\rightarrow\text{BF}_3) = 12{\cdot}5$ kcal./mole; cf. Skinner and Smith, *J.*, 4025, 1953], coupled with the fact the methyl chloride (and alkyl chlorides generally) does not form a complex with boron trifluoride at all. However, some factors which influence the strength of donor–acceptor bonding (*e.g.*, change of shape in the acceptor molecule, steric interactions) are not relevant to back-co-ordination, and we would not overstress the parallelism we have noted or suggest that it should hold generally.

The conclusions reached in this paper could be further tested by a thermochemical study on the dimethylaminoethoxyborines. Neither of the compounds $\text{B(OEt)}_2\text{NMe}_2$, $\text{B(NMe}_2)_2\text{OEt}$, appears to have been described and an attempt to prepare the former, by interaction of $\text{B(OEt)}_2\text{Cl}$ with excess of dimethylamine, gave a 2 : 1 mixture of triethyl borate and trisdimethylaminoborine. This suggests that $\text{B(OEt)}_2\text{NMe}_2$ (if formed at all) is disproportionated when heated, but further work is needed to establish this.

Finally, it should be emphasized that the explanation we have given of the heats of redistribution begins from the assumption that they are to be attributed *entirely* to back-co-ordination. This may be an oversimplification of the problem (cf. Skinner, *Rec. Trav. chim.*, in the press) in that other factors—of which steric interaction between the relatively bulky Cl atoms may be one of the more important—are neglected.

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Phthalaldehydes and Related Compounds. Part VI. Further Studies on Vicinal Carboxyphthalaldehydes.*

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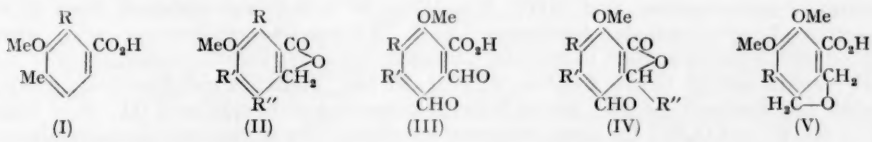
The syntheses of 3-formyl-4-methylopianic acid and 3-formyl-4-methoxyopianic acid by the action of *N*-bromosuccinimide on the corresponding substituted 5 : 6-dimethoxyphthalan-4-carboxylic acids, obtained respectively from 5-methylmeconin and 5 : 6 : 7-trimethoxyphthalide, are described. A more detailed examination of the 4-hydroxymethylphthalide–carboxyphthalan rearrangement (Brown and Newbold, *J.*, 1952, 4878) has been made and its mechanism is discussed.

THIS paper is a continuation of studies on the synthesis of vicinal carboxy-*o*-phthalaldehydes related to gladiolic acid (III; R = Me, R′ = H) tautomeric with (IV; R = Me, R′ = H, R″ = OH), the antifungal metabolic product of *Penicillium gladioli* Machacek (see Brown and Newbold, *J.*, 1954, 1076, for references). It was desirable to prepare such compounds in order to obtain more evidence concerning the relation between structure and fungistatic activity (see Grove, *Biochem. J.*, 1953, **54**, 664). The preparation of 3-formyl-4-methylopianic acid (III; R = OMe, R′ = Me), tautomeric with (IV; R = OMe, R′ = Me, R″ = OH), and 3-formyl-4-methoxyopianic acid (III; R = R′ = OMe), tautomeric with (IV; R = R′ = OMe, R″ = OH), was therefore undertaken.



The starting material for the synthesis of (III; R = OMe, R′ = Me) was 6-methoxy-5-methylphthalide (II; R = R″ = H, R′ = Me) which was readily obtained by the action of formaldehyde and hydrochloric acid on 3-methoxy-*p*-toluic acid (I; R = H) (Charlesworth, Rennie, Sinder, and Yan, *Canad. J. Res.*, 1945, **23**, *B*, 17). Nitration of (II; R = R″ = H, R′ = Me) gave 6-methoxy-5-methyl-7-nitrophthalide (II; R = NO_2, R′ = Me, R″ = H), the orientation of the nitro-group being apparent from subsequent reactions of the compound. The nitrophthalide was hydrogenated in the presence of nickel to the amine, and the amino-group was converted, *via* the iodo-group, into the methoxy-group, giving 5-methylmeconin (II; R = OMe, R′ = Me, R″ = H), m. p. 82·5°, using the method developed by McRae, Van Order, Griffiths, and Habgood (*Canad. J. Chem.*, 1951, **29**, 482; cf. Manske, McRae, and Moir, *ibid.*, p. 526) for the synthesis of 5 : 6 : 7-trimethoxyphthalide. If nitration of (II; R = R″ = H, R′ = Me) had taken place in the 4-position, the derived methoxy-compound would have been 4 : 6-dimethoxy-5-methylphthalide (II; R = H, R′ = Me, R″ = OMe); this compound, m. p. 158°, has been prepared from 3 : 5-dimethoxy-*p*-toluic acid (CO_2H = 1) independently by Asahina and Hayashi (*Ber.*, 1933, **66**, 1023) and Charlesworth and Robinson (*J.*, 1934, 1531). Thus nitration of 6-methoxy-5-methylphthalide is comparable with that of *m*-meconin (II; R = R″ = H, R′ = OMe) which gave the 7-nitro-derivative (II; R = NO_2, R′ = OMe, R″ = H) (Ray and Robinson, *J.*, 1925, 1621) and that of (I; R = H) which gave (I; R = NO_2) (Simonsen and Rau, *J.*, 1921, 1339); these reactions demonstrate the powerful directive influence into the vicinal position of the methoxy-group *meta*-substituted to the carboxyl group, an example of the general behaviour where a group of the $+E$ type is substituted in the *meta*-position to one of the $-I - M$ type (Ingold, "Structure and Mechanism in Organic Chemistry," Bell, London, 1953, pp. 267, 268).

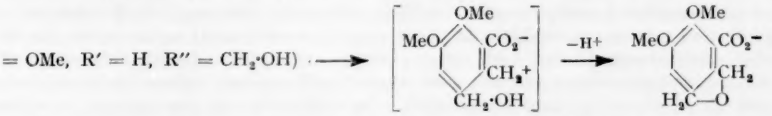
* Part V, *J.*, 1954, 1836.

Chloromethylation of 5-methylmeconin gave the 4-chloromethyl derivative (II; R = OMe, R′ = Me, R″ = CH_2Cl), m. p. 118—121°, different from the product, 7-chloromethyl-4 : 6-dimethoxy-5-methylphthalide (II; R = CH_2Cl, R′ = Me, R″ = OMe), m. p. 130—131°, obtained by the action of formaldehyde and hydrochloric acid on 3 : 5-dimethoxy-*p*-toluic acid (Charlesworth, Rennie, Sinder, and Yan, *loc. cit.*); this is further evidence of the correctness of our orientation in (II; R = NO_2, R′ = Me, R″ = H). The chloromethyl compound on reduction with zinc gave 4 : 5-dimethylmeconin (II; R = OMe, R′ = R″ = Me). In Part I of this series (Brown and Newbold, *J.*, 1952, 4878) heating 4-chloromethylmeconin (II; R = OMe, R′ = H, R″ = CH_2Cl) with aqueous sodium carbonate was shown to yield 4-hydroxymethylmeconin (II; R = OMe, R′ = H, R″ = CH_2·OH) which underwent a novel isomerisation, on being heated with aluminium *tert.*-butoxide in benzene, to give 5 : 6-dimethoxyphthalan-4-carboxylic acid (V; R = H), the reverse process being effected by the action of hot dilute mineral acid. On similar hydrolysis by carbonate 4-chloromethyl-5-methylmeconin gave 5 : 6-dimethoxy-7-methylphthalan-4-carboxylic acid (V; R = Me) as the major product with some 4-hydroxymethyl-5-methylmeconin (II; R = OMe, R′ = Me, R″ = CH_2OH); the yield of the former product was increased by prolonging the reaction time and 5 : 6-dimethoxy-7-methylphthalan-4-carboxylic acid could be isomerised to 4-hydroxymethyl-5-methylmeconin by heating it with mineral acid. Attempts to convert 4-chloromethyl-5-methylmeconin into 3-formyl-4-methylopianic acid by the action of *N*-bromosuccinimide followed by hydrolysis, an effective method for the formation of 3-formylopianic acid (III; R = OMe, R′ = H), tautomeric with (IV; R = OMe, R′ = H, R″ = OH), were unsuccessful, no crystalline product being obtained. Attention was then turned to the alternative approach (*loc. cit.*), that of treating the carboxyphthalan with *N*-bromosuccinimide with subsequent hydrolysis of the intermediate; by this means 3-formyl-4-methylopianic acid (III; R = OMe, R′ = Me) was obtained from 5 : 6-dimethoxy-7-methylphthalan-4-carboxylic acid. 3-Formyl-4-methylopianic acid, when heated with aqueous sodium hydroxide, undergoes the characteristic isomerisation to the carboxyphthalide (cf. Grove, *Biochem. J.*, 1952, **50**, 648; Raistrick and Ross, *ibid.*, p. 635; Brown and Newbold, *loc. cit.*), giving 5-methylmeconin-4-carboxylic acid (II; R = OMe, R′ = Me, R″ = CO_2H); the same compound was obtained by oxidation of 5 : 6-dimethoxy-7-methylphthalan-4-carboxylic acid with chromium trioxide.

The preparation of 3-formyl-4-methoxyopianic acid (III; R = R′ = OMe) utilised 5 : 6 : 7-trimethoxyphthalide (II; R = R′ = OMe, R″ = H) (McRae *et al.*, *loc. cit.*) as starting material. Though no homogeneous product could be obtained by the action of formaldehyde and hydrochloric acid on this phthalide under the usual reflux conditions, the mild ones used by Wilson, Zirkle, Anderson, Stehle, and Ullyot (*J. Org. Chem.*, 1951, **16**, 792) for the conversion of *o*-veratric acid into meconin, gave 4-chloromethyl-5 : 6 : 7-trimethoxyphthalide (II; R = R′ = OMe, R″ = CH_2Cl) in excellent yield. Sodium carbonate hydrolysis of the chloromethyl derivative gave 4-hydroxymethyl-5 : 6 : 7-trimethoxyphthalide (II; R = R′ = OMe, R″ = CH_2·OH) and 5 : 6 : 7-trimethoxyphthalan-4-carboxylic acid (V; R = OMe), the proportion of the latter compound being increased by prolongation of the reaction time. The acid (V; R = OMe) was isomerised to 4-hydroxymethyl-5 : 6 : 7-trimethoxyphthalide by hot mineral acid while the reverse change could be partially achieved by means of sodium carbonate. The action of *N*-bromosuccinimide on the acid (V; R = OMe), followed by hydrolysis of the product, afforded 3-formyl-4-methoxyopianic acid (III; R = R′ = OMe) in good yield. Isomerisation of (III; R = R′ = OMe) by alkali gave 5 : 6 : 7-trimethoxyphthalide-4-carboxylic acid (II; R = R′ = OMe, R″ = CO_2H).

In order to gain information on the hydroxymethylphthalide–carboxyphthalan rearrangement the behaviour of 4-hydroxymethylmeconin with different bases was studied. The isomerisation of 4-hydroxymethylmeconin to 5 : 6-dimethoxyphthalan-4-carboxylic acid was achieved in 8% yield by heating with aqueous sodium hydroxide, in 31% yield by prolonged heating with sodium carbonate, in 39% yield by heating with sodium methoxide in benzene, in 60% yield by heating with aluminium *tert.*-butoxide in benzene (Brown and Newbold, *loc. cit.*), and in quantitative yield by using sodium methoxide in methanol. It is notable that in the last reaction no ester was formed and it is suggested that the course of

the rearrangement consists in the opening of the lactone ring of 4-hydroxymethylmeconin between the methylene group and the adjacent oxygen atom, giving a sodium salt bearing an intermediate carbonium ion which then forms the phthalan ring by interaction with the 4-hydroxymethyl group with loss of a proton :



A precedent is found in the reaction of phthalide with potassium cyanide, giving the salt of *o*-carboxyphenylacetonitrile (Wislicenus, *Annalen*, 1886, **233**, 102), which may involve an intermediate carbonium ion.

The dissociation constants of some of the acids described in this paper have been measured. 5 : 6-Dimethoxyphthalan-4-carboxylic acid has pK_a 3·5, its 7-methyl derivative pK_a 3·75, and its 7-methoxy-derivative pK_a 3·73; the 7-substituents thus increase electron-availability in the *para*-position, though their effects on acidic strength are in reverse order compared with the strengths of *p*-toluic acid and *p*-anisic acid (Dippy, *Chem. Reviews*, 1939, **25**, 151). The acidic strengths, pK_a, of 3-formyl-4-methylopianic acid and 3-formyl-4-methoxyopianic acid are respectively 3·5 and 3·8. Comparison with the pK_a of 3-formylopianic acid (4·3) indicates that the effect of substitution in the 5-position does not follow the normal effect of substitution on the strengths of benzoic acid derivatives and is no doubt complicated by interaction between the 5-substituent and the tautomeric phthalaldehydic acid system.

Experimental

Ultra-violet absorption spectra were determined in ethanol solution, unless otherwise stated, with a Unicam S.P.500 spectrophotometer. The pK_a values (classical) and equivalents were determined in water potentiometrically under nitrogen, according to the micro-method of Catch, Cook, and Kitchener (*J.*, 1945, 319), 0·05N-sodium hydroxide being used with an initial 0·10M-concentration of acid.

6-*Methoxy*-5-*methyl*-7-*nitrophthalide* (with W. Laird).—Finely divided 6-methoxy-5-methylphthalide (Charlesworth, Rennie, Sinder, and Yan, *loc. cit.*; 5 g.) was added during 5 min. to a stirred mixture of nitric acid (16 c.c.; *d* 1·5) and acetic anhydride (24 g.) at 0°. When all the phthalide had dissolved, the solution was poured on ice, and the solid separated, washed with water, and crystallised from ethanol, to give 6-*methoxy*-5-*methyl*-7-*nitrophthalide* (4·5 g., 73%) as needles, m. p. 146° (Found : C, 54·2; H, 4·1. $C_{10}H_9O_5N$ requires C, 53·8; H, 4·1%). Light absorption : Max. at 2080 (ε 28,800) and 2890 (ε 2650); inflexion at 2410 Å (ε 6800).

7-*Amino*-6-*methoxy*-5-*methylphthalide* (with W. Laird).—A solution of 6-methoxy-5-methyl-7-nitrophthalide (2 g.) in ethyl acetate (200 c.c.) was shaken with hydrogen at room temperature and atmospheric pressure in the presence of freshly prepared Raney nickel (1·2 g.; W.6, *Org. Synth.*, **29**, 24). When absorption was complete (*ca.* 15 min.) the mixture was filtered, the filtrate evaporated to dryness under reduced pressure, and the residual solid crystallised from benzene–light petroleum (b. p. 60—80°) from which 7-*amino*-6-*methoxy*-5-*methylphthalide* (1·7 g.) separated as needles, m. p. 109—110° (Found : C, 62·5; H, 5·65. $C_{10}H_{11}O_3N$ requires C, 62·2; H, 5·7%). Light absorption : Max. at 2340 (ε 34,700), 2500 (ε 7800), and 3280 Å (ε 5700).

7-*Iodo*-6-*methoxy*-5-*methylphthalide*.—The foregoing aminophthalide (4 g.) in sulphuric acid (3 c.c.; *d* 1·84) and water (20 c.c.) was diazotized at 0° with sodium nitrite (2 g.). After the addition of urea, a solution of potassium iodide (4 g.) in water (15 c.c.) was added and the mixture kept at room temperature for 3 hr. and then heated on the steam-bath for 10 min. After cooling, the solid was separated and crystallised from ethanol (charcoal), to give 7-*iodo*-6-*methoxy*-5-*methylphthalide* (3·4 g.) as needles, m. p. 117—118° (Found : C, 39·3; H, 3·1. $C_{10}H_9O_3I$ requires C, 39·5; H, 3·0%). Light absorption : Max. at 2220 (ε 28,000), 2460 (ε 9000), and 3020 Å (ε 4700).

5-*Methylmeconin*.—The iodo-compound (3·2 g.) and copper bronze (100 mg.) were added to a solution of potassium methoxide from potassium (0·9 g.) and dry methanol (50 c.c.) and the mixture was refluxed for 24 hr. The filtered solution was diluted with water (25 c.c.), made

acid (Congo-red) with 5N-hydrochloric acid, and extracted with ether (3 × 50 c.c.). The combined ethereal extract was washed with water, dried (Na_2SO_4), and evaporated, and the residue crystallised from light petroleum (b. p. 40—60°), to yield 5-*methylmeconin* (1·6 g.) as felted needles, m. p. 82·5° (Found : C, 63·1; H, 5·85. $C_{11}H_{12}O_4$ requires C, 63·45; H, 5·8%). Light absorption : Max. at 2130 (ε 29,600), 2460 (ε 8300), and 2960 Å (ε 3000).

4-*Chloromethyl*-5-*methylmeconin*.—5-Methylmeconin (400 mg.), hydrochloric acid (5 c.c.; *d* 1·16), and aqueous formaldehyde (3 c.c.; 40%) were heated under reflux for 30 min. The cooled mixture was diluted with water (10 c.c.) and extracted with chloroform (3 × 10 c.c.). The combined chloroform extracts were washed with aqueous sodium hydrogen carbonate, then water, dried (Na_2SO_4), and evaporated. Crystallisation of the residue from benzene–light petroleum (b. p. 60—80°) gave 4-*chloromethyl*-5-*methylmeconin* (250 mg.) as needles, m. p. 118—121° (Found : C, 56·4; H, 5·3. $C_{12}H_{13}O_4Cl$ requires C, 56·15; H, 5·1%). Light absorption : Max. at 2190 (ε 40,100) and 3050 (ε 3800); inflexion at 2420—2480 Å (ε 9700).

4 : 5-*Dimethylmeconin*.—4-Chloromethyl-5-methylphthalide (200 mg.) in ethanol (5 c.c.; 95%) was heated under reflux with zinc dust (250 mg.) and treated with hydrochloric acid (2·5 c.c.; *d* 1·16) added in portions during 2 hr. The mixture was evaporated under reduced pressure; water was added and the product isolated by means of ether. Removal of the ether and crystallisation of the residue from hexane gave 4 : 5-*dimethylmeconin* (100 mg.) as prisms, m. p. 110° (Found : C, 65·2; H, 6·5. $C_{12}H_{14}O_4$ requires C, 64·85; H, 6·35%). Light absorption : Max. at 2160 (ε 28,800), 2480 (ε 11,000), and 3000 Å (ε 3900).

5 : 6-*Dimethoxy*-7-*methylphthalan*-4-*carboxylic Acid*.—4-Chloromethyl-5-methylmeconin (100 mg.) was heated under reflux with a solution of anhydrous sodium carbonate (400 mg.) in water (6 c.c.) for 1½ hr. The cooled solution was made acid to Congo-red with 3N-hydrochloric acid and extracted with chloroform (3 × 10 c.c.), The combined, dried (Na_2SO_4) extracts were evaporated and the residue was crystallised from aqueous ethanol, to give 5 : 6-*dimethoxy*-7-*methylphthalan*-4-*carboxylic acid* (75 mg.) as plates, m. p. 156—157° (Found : C, 60·7; H, 5·9%); equiv., 232. $C_{12}H_{14}O_5$ requires C, 60·5; H, 5·9%; equiv., 238). The compound sublimed unchanged at 120°/10^{-4} mm. and showed light absorption : Max. at 2120 (ε 29,000), 2420 (ε 7400), and 2960 Å (ε 2800). Under the same conditions save that heating was carried out for ½ hr., 4-chloromethyl-5-methylmeconin (400 mg.) gave 5 : 6-dimethoxy-7-methylphthalan-4-carboxylic acid (130 mg.) and 4-hydroxymethyl-5-methylmeconin (70 mg.), the separation being achieved by use of chloroform and aqueous sodium hydrogen carbonate.

4-*Hydroxymethyl*-5-*methylmeconin*.—The foregoing phthalan acid (100 mg.) was heated under reflux with 5N-hydrochloric acid (4 c.c.) for 1 hr. The cooled solution was extracted with chloroform (3 × 10 c.c.), the combined extracts were dried (Na_2SO_4) and evaporated, and the residue crystallised from benzene–light petroleum (b. p. 60—80°) to give 4-*hydroxymethyl*-5-*methylmeconin* (60 mg.) as needles, m. p. 101—102° (Found : C, 60·6; H, 4·7. $C_{12}H_{14}O_5$ requires C, 60·5; H, 5·9%). Light absorption : Max. at 2140 (ε 41,000), 2470 (ε 9100), and 2990 Å (ε 3600).

3-*Formyl*-4-*methylopianic Acid*.—A solution of 5 : 6-dimethoxy-7-methylphthalan-4-carboxylic acid (200 mg.) in dry benzene (12 c.c.) and dry carbon tetrachloride (12 c.c.) was refluxed with *N*-bromosuccinimide (2·25 mols.) for 15 min. with irradiation from a 60-w lamp. The cold mixture was filtered, the filtrate evaporated under reduced pressure, and the remaining oil heated with water (10 c.c.) on the steam-bath while being stirred for 1½ hr. Isolation by use of chloroform gave an acid fraction which crystallised from benzene, to yield 3-*formyl*-4-*methylopianic acid* (77 mg.) as needles, m. p. 145—146° (Found : C, 57·0; H, 5·0%; equiv., 247. $C_{12}H_{12}O_6$ requires C, 57·1; H, 4·8%; equiv., 252). Light absorption in water : Max. at 2070 (ε 29,600) and 2800 Å (ε 2000). 3-Formyl-4-methylopianic acid dissolves in concentrated sulphuric acid, giving a yellow-brown solution; on exposure to ammonia vapour the solid becomes brown and resinifies; it becomes pink on prolonged exposure to light.

5-*Methylmeconin*-4-*carboxylic Acid*.—(*a*) A solution of 5 : 6-dimethoxy-7-methylphthalan-4-carboxylic acid (200 mg.) in glacial acetic acid (5 c.c.) was treated with chromium trioxide (200 mg.) in glacial acetic acid (5 c.c.) during 1 min. with stirring. After 5 min. the mixture was diluted with water (10 c.c.) and extracted with chloroform (3 × 15 c.c.). The combined extracts were washed with sodium hydrogen carbonate (30 c.c.; 10%); acidification of this extract with 5N-hydrochloric acid and isolation with chloroform gave 5-*methylmeconin*-4-*carboxylic acid* (100 mg.) which separated from aqueous ethanol as needles, m. p. 195—196·5° (Found : C, 57·3; H, 4·9. $C_{12}H_{12}O_6$ requires C, 57·1; H, 4·8%). Light absorption : Max. at 2200 (ε 31,200) and 3000 Å (ε 3200).

(*b*) 3-Formyl-4-methylopianic acid (25 mg.) in 3N-sodium hydroxide (10 c.c.) was refluxed for 30 min. The cooled mixture was extracted with chloroform; no neutral fraction was obtained

from the extract. Acidification of the alkaline solution (Congo-red) with 5N-hydrochloric acid gave 5-methylmeconin-4-carboxylic acid (12 mg.) which crystallised from aqueous ethanol as needles, m. p. and mixed m. p. 195—196·5°.

4-Chloromethyl-5 : 6 : 7-trimethoxyphthalide.—A suspension of 5 : 6 : 7-trimethoxyphthalide (McRae *et al., loc. cit.*) (1·0 g.) in hydrochloric acid (2 c.c.; *d* 1·16) and aqueous formaldehyde (1 c.c.; 40%) was treated with gaseous hydrogen chloride at 0° until solution was complete (*ca.* 10 min.). After being kept overnight at room temperature the solution was diluted with water and the product isolated by means of chloroform. Crystallisation from light petroleum (b. p. 60—80°) gave *4-chloromethyl-5 : 6 : 7-trimethoxyphthalide* (1·1 g.) as needles, m. p. 82·5° (Found : C, 52·7; H, 4·9. $C_{12}H_{13}O_5Cl$ requires C, 52·85; H, 4·8%). Light absorption : Max. at 2240 (ε 39,200) and 2970 (ε 2900); inflexion at 2420—2520 Å (ε 8300).

Sodium Carbonate Treatment of 4-Chloromethyl-5 : 6 : 7-trimethoxyphthalide.—A solution of sodium carbonate (500 mg.) in water (10 c.c.) was refluxed for ½ hr. with 4-chloromethyl-5 : 6 : 7-trimethoxyphthalide (200 mg.). After acidification and extraction with chloroform (3 × 10 c.c.) the combined extracts were separated into acid and neutral fractions by using sodium hydrogen carbonate solution. The former fraction crystallised from benzene–light petroleum (b. p. 60—80°) to give 5 : 6 : 7-*trimethoxyphthalan-4-carboxylic acid* (60 mg.) as prisms, m. p. 125—126° (Found : C, 57·0; H, 5·8%; equiv., 254. $C_{12}H_{14}O_6$ requires C, 56·7; H, 5·55%; equiv., 254). Light absorption : Max. at 2160 (ε 31,200), 2530 (ε 9800), and 2940 Å (ε 2700). The neutral fraction separated from the same solvents, to give *4-hydroxymethyl-5 : 6 : 7-trimethoxyphthalide* (80 mg.) as needles, m. p. 73° (Found : C, 56·3; H, 5·8. $C_{12}H_{14}O_6$ requires C, 56·7; H, 5·55%). Light absorption : Max. at 2180 (ε 36,400), 2520 (ε 9950), and 2960 Å (ε 3000).

When 4-chloromethyl-5 : 6 : 7-trimethoxyphthalide (500 mg.) was refluxed for 2 hr. with sodium carbonate (1·0 g.) in water (15 c.c.), and the products were isolated as above, 5 : 6 : 7-trimethoxyphthalan-4-carboxylic acid (340 mg.) and 4-hydroxymethyl-5 : 6 : 7-trimethoxyphthalide (110 mg.) were obtained. The latter compound (140 mg.), when refluxed for ½ hr. with sodium carbonate (500 mg.) in water (10 c.c.), gave the corresponding carboxyphthalan (60 mg.), the remainder being unchanged. 5 : 6 : 7-Trimethoxyphthalan-4-carboxylic acid (100 mg.) was refluxed with hydrochloric acid (40 c.c.; 3N) for 2 hr. and 4-hydroxymethyl-5 : 6 : 7-trimethoxyphthalide (55 mg.), m. p. and mixed m. p. 73°, isolated in the usual way.

3-Formyl-4-methoxyopianic Acid.—5 : 6 : 7-Trimethoxyphthalan-4-carboxylic acid (250 mg.) in benzene (12 c.c.) and carbon tetrachloride (12 c.c.) was refluxed for 20 min. with *N*-bromosuccinimide (2·2 mols.) with irradiation from a 60-w lamp. Further treatment as described for 3-formyl-4-methylopianic acid gave *3-formyl-4-methoxyopianic acid* (130 mg.) which separated from benzene as needles, m. p. 146° (Found : C, 53·55; H, 4·7%; equiv., 262. $C_{12}H_{12}O_7$ requires C, 53·7; H, 4·5%; equiv., 268). Light absorption in water : Max. at 2080 (ε 32,400); inflexion at 2700—2750 Å (ε 2100). The compound dissolves in concentrated sulphuric acid giving a yellow solution; on exposure to ammonia vapour the solid becomes brown and resinifies.

5-Methoxymeconin-4-carboxylic Acid.—3-Formyl-4-methoxyopianic acid (100 mg.) was refluxed in 3N-sodium hydroxide (30 c.c.) for 30 min. Isolation by means of chloroform gave *5-methoxymeconin-4-carboxylic acid* (70 mg.) which separated from benzene as needles, m. p. 176° (Found : C, 53·9; H, 4·6. $C_{12}H_{12}O_7$ requires C, 53·7; H, 4·5%). Light absorption : Max. at 2270 (ε 36,000) and 3000 (ε 3300); inflexion at 2530—2560 Å (ε 10,400).

5 : 6-Dimethoxyphthalan-4-carboxylic Acid (with D. H. Kenny).—(*a*) 4-Hydroxymethylmeconin (0·5 g.) was heated under reflux for 7¼ hr. with a solution of sodium methoxide in anhydrous methanol, from sodium (0·25 g.) and methanol (11 c.c.). The solution was diluted with water, made acid to Congo-red with dilute hydrochloric acid, and extracted with chloroform. The chloroform extracts were washed with aqueous sodium hydrogen carbonate, then water, dried (Na_2SO_4), and evaporated, giving no residue. Acidification of the alkaline washings and isolation of the product by use of chloroform gave 5 : 6-dimethoxyphthalan-4-carboxylic acid (0·5 g.), which separated from water as needles, m. p. 148—149° alone or mixed with Brown and Newbold's sample (*loc. cit.*).

(*b*) 4-Hydroxymethylmeconin (0·5 g.) in dry benzene (10 c.c.) was heated under reflux for 18 hr. with sodium methoxide (0·5 g.). Isolation in the usual way gave 4-hydroxymethylmeconin (264 mg.), m. p. and mixed m. p. 126—128° and 5 : 6-dimethoxyphthalan-4-carboxylic acid (194 mg., 39%), m. p. and mixed m. p. 148—149°.

(*c*) 4-Hydroxymethylmeconin (1·0 g.) was heated on the steam-bath for 7¼ hr. in 3N-sodium hydroxide (15 c.c.). Isolation gave unchanged material (840 mg.) and 5 : 6-dimethoxyphthalan-4-carboxylic acid (110 mg., 8%), m. p. and mixed m. p. 146—148°. Brown and Newbold (*loc.*

cit.) reported that 4-hydroxymethylmeconin was unchanged after 2 hours' boiling with 3N-sodium hydroxide.

(*d*) 4-Hydroxymethylmeconin (1·0 g.) was heated under reflux for 7½ hr. with a solution of anhydrous sodium carbonate (2·5 g.) in water (25 c.c.). Isolation gave starting material (700 mg.) and 5 : 6-dimethoxyphthalan-4-carboxylic acid (300 mg., 31%), m. p. and mixed m. p. 145—147°.

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Chemistry of the Coprosma *Genus. Part VIII.* The Occurrence of Asperuloside.*

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Asperuloside has been shown by isolation or by colour reactions to occur in 73 *Coprosma* species. Additional occurrences in other species of the *Rubiaceae* are listed.

ASPERULOSIDE has been isolated in crystalline form from six members of the *Rubiaceae* family. On the basis of the test that on hydrolysis it gives first a green colour and then a black precipitate it has been detected in 14 other members of this family. It has been isolated from one member of the *Euphorbiaceae*. It is moreover probably identical with rubichloric acid (chlorigenin) which was obtained as a syrup from four other members of the *Rubiaceae*.

We have now isolated asperuloside from five *Coprosma* species (*Rubiaceae*), have detected its presence by colour reactions in 68 other species of this genus, and failed to detect in two others. We also record positive tests for 43 other plants, and negative tests for 57 others. Details of these and the earlier isolations are in the Experimental section.

The stability of asperuloside is indicated by the fact that the specimen of *C. solandri* Kirk collected by Banks and Solander during Captain Cook's visit to New Zealand in 1769 still gave a positive test.

Hérissey (*Compt. rend.*, 1925, **180**, 1695) described asperuloside as colourless, hydrated needles, m. p. 126—127°, $[\alpha]_D^{25}$ −195·5 (in H_2O), *M*, 410 (cryoscopic in water). No formula was suggested, but it was shown that a reducing sugar, presumed to be glucose, was produced on both acid and enzymic (emulsin) hydrolysis. Juillet, Susplugas, and Massa (*J. Pharm. Chim.*, 1938, **27**, 56) identified the sugar as glucose. The aglycone, asperuligenol, was an amorphous blackish-brown precipitate similar to that formed by the hydrolysis of aucubin (Bourquelot and Hérissey, *Ann. Chim. Phys.*, 1905, **4**, 289). Trim and Hill (*Biochem. J.*, 1951, **50**, 310) suggested a formula $C_{17}H_{24}O_{11}$ for asperuloside and prepared an acetyl derivative, m. p. 153°, regarded as the octa-acetate. Because of the similarity in colour reactions they suggested that asperuloside was a furan derivative similar to aucubin whose constitution has been elucidated by Karrer and Schmid (*Helv. Chim. Acta*, 1946, **29**, 525).

Asperuloside, as obtained by us, has m. p. 131—132°, after softening at 126°, the m. p. recorded by Hérissey. Combustions of the air-dried material indicate the formula $C_{18}H_{24}O_{12}$, which, from Hérissey's and our results, represent the hydrate, $C_{18}H_{22}O_{11},H_2O$. Since asperuloside is a glucoside it may be further represented as $C_{12}H_{11}O_5{\cdot}O{\cdot}C_6H_{11}O_5,H_2O$, the glucose being joined by a β-linkage since it is hydrolysed by emulsin. An acetate prepared by Nicholls (Theses, Univ. of New Zealand, 1946, 1948), m. p. 154°, is regarded as the tetra-acetate, $C_{18}H_{18}O_7(O{\cdot}CO{\cdot}CH_3)_4$. A tribenzoate has also been prepared. Degradative studies leading to the constitution will be reported later.

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Experimental

Analyses are by Mr. R. N. Seelye of this Department and Dr. J. A. Mills, University of Adelaide.

Plant Sources of Asperuloside.—Asperuloside was first isolated in crystalline form by Hérissey (*Compt. rend.*, 1925, **180**, 1695; *J. Pharm. Chim.*, 1925, **2**, 177) from *Asperula odorata* (woodruff) and later from *Galium aparine* (*Compt. rend.*, 1926, **182**, 865; *Bull. Soc. Chim. biol.*, 1926, **8**, 489, 1208), *G. verum* (*Compt. rend.*, 1927, **184**, 1674), and *Coprosma repens* (syn. *C. baueriana*) (*J. Pharm. Chim.*, 1933, **17**, 553). Hérissey (*Bull. Soc. Chim. biol.*, 1926, **8**, 1208) considered that asperuloside is probably identical with rubichloric acid (chlorogenin), obtained only as a syrup by Rochleder (*Ann. Chim. Phys.*, 1851, **80**, 321) from *Rubia tinctorum* (madder), by Orth (*J. pr. Chem.*, 1855, **64**, 10) from *Gardenia grandiflora*, and by Perkin and Hummel (*J.*, 1893, **63**, 1160) from *Oldenlandia umbellata* (Indian madder) and *Morinda umbellata* (*J.*, 1894, **65**, 851). The identification was based on the characteristic reaction of asperuloside on acid hydrolysis, giving first a green colour and then a black precipitate. The same reaction was used by Hérissey (*Compt. rend.*, 1926, **182**, 865; 1927, **184**, 1674) to detect the presence of asperuloside in *Asperula tinctoria, Coprosma lucida, C. robusta, Crucianella stylosa, Galium cruciata, G. mollugo, Leptodermis lanceolata, Manettia bicolor, Paederia foetida, Putoria calabarica, Rubia peregrina, R. tinctorum, Serissa foetida*, and *Sherardia arvensis*. Juillet *et al.* (*loc. cit.*) isolated asperuloside from *Crucianella maritima* and *C. angustifolia*. All the above species are members of the *Rubiaceae*. More recently, however, Trim (*Nature*, 1951, **167**, 485; Trim and Hill, *loc. cit.*) isolated it from *Daphniphyllum macropodum*, a member of the *Euphorbiaceae*.

By acetone extraction we have isolated asperuloside from *Coprosma arborea* Kirk, *C. lucida* J. R. & G. Forst., *C. repens* Rich., *C. robusta* Raoul, and *C. tenuifolia* Cheesem., and through its characteristic colour reactions we have detected it in 68 other *Coprosma* species. These include all the species listed by Oliver (Bernice P. Bishop Museum Bull. 132, 1935, p. 202) with the exception of *C. baueri* Endl. and *C. benefica* Oliv., which gave negative tests, and *C. glabrata* Moore, *C. hookeri* (Don) Oliv., *C. moorei* Rod., *C. nivalis* Oliv., *C. novaehebridae* Oliv., *C. oceanica* Oliv., *C. persicaefolia* Gray, *C. pyrifolia* (Hook. & Arn.) Skotts., *C. raiateensis* Moore, *C. rapensis* Brown, *C. serrata* St. John, *C. setosa* Moore, *C. tadgelli* Oliv., *C. ternata* Oliv., and *C. wollastonii* Wern., which were not available.

Positive colour reactions characteristic of asperuloside were obtained from the following other members of the *Rubiaceae* : *Asperula perpusilla* Hook. f., *Diodia teres* Walt., *D. virginica* L., *Galium tenuicaule* A. Cunn., *Gardenia remyi* Mann, *Gouldia axillaris* Wawra, *G. purpurea* (Fosb.) Skottsb., *G. st.-johnii* Fosb., *G terminalis* (Hook. & Arn.) Hilleb. [including many varieties and forms described by Fosberg (Bernice P. Bishop Museum Bull. 147, 1937)], *Hedyotis acuminata* (Cham. & Schl.) Stend. f. *grayana* Fosb., *H. acuminata* (Cham. & Schl.) Stend. f. *sherffiana* Fosb., *H. angusta* Fosb. var. *umbrosa* Fosb., *H. centranthoides* (Hook. & Arn.) Stend., *H. elmeri* Merr., *H. fluviatilis* (Forbes) Fosb. var. *kamopuaana* (Degen) Fosb. f. *hathewayi* Fosb., *H. glaucifolia* (Gray) Fosb. var. *waimeae* (Wawra) Fosb., *H. schlechtendahliana* Stend. var. *cordata* (Cham. & Schl.) Fosb., *H. schlechtendahliana* Stend. var. *glabrescens* Fosb., *H. schlechtendahliana* Stend. f. *kaalensis* Fosb., *H. uniflora* DC., *H. vestita* R. Br., *Houstonia purpurea* L., *Kadua centranthoides* Hook. & Arn., *K. glomerata* Hook. & Arn., *K. grandis* A. Gray, *K. longipedunculata* Skottsb., *Mitchella repens* L., *Morinda bucidaefolia* A. Gray, *M. citrifolia* L., *M. forsteri* Seem., *M. rojoc* L., *M. trimera* Hillebr. var. *sanwicense* (Deg.) Skottsb., *M. umbellata* L., *Nertera cunninghamii* Hook. f., *N. depressa* Gaertn., *Normandia neo-caledonica* Hook. f., *Oldenlandia foetida* Forst. f., *Opercularia varia* Hook. f., *Oreopolus citrinus* Sch., *Paederia pringlei* Greenm., *Richardsonia scabra* A. St. Hil., *Spermacoce glabra* Michx., *Straussia hawaiiensis* A. Gray.

Negative tests were obtained from the following species which gave yellow, pink, red, reddish-brown colours or were without colour : *Asperula capitata* Kit., *A. ciliata* Roch., *A. aristata* L., *A. cynanchica* L., *A. galioides* DC., *A. taurina* L., *A. tenella* Boiss., *Bikkia grandiflora* Reinw., *Bobea elatior* Gand., *Bouvardia capitata* Bull., *Canthium odoratum* (Forst.) Seem., *Cephalanthus occidentalis* L., *Chiococca racemosa* Jacq., *Coffea arabica* L., *C. oxyloba* Janka, *Cruckshanksia hymenodon* Hook. & Arn., *Dentella repens* Forst., *Dolicholobium* sp., *Galium umbrosum* Forst., *Gardenia brighamii* Mann, *G. kaitensis* DC., *Guettarda ambigua* DC., *G. blodgettii* Shuttl., *G speciosa* L., *Hamelia patens* Jacq., *Hedyotis hispida* Retz., *H. microphylla* Merr., *H. schlechtendahliana* Stend. var. *rigida* Fosb., *Hintonia latiflora* (DC). Bull. var. *leiantha* Bull., *Ixora bracteata* Cheesem., *I. coccinea* L., *I. cumingiana* Vid., *Morinda bracteata* Roxb., *Mussaenda frondosa* L., *Nertera dichondrifolia* (A. Cunn.) Hook. f., *N. setulosa* Hook. f., *Ophiorrhiza leptantha* A. Gray, *Plectronia barbata* Benth. & Hook., *P. peduncularis* (Cav.) Vid., *Psychotria bullata* Seem., *P.*

confertiloba A. C. Sm., *P. forsteriana* A. Gray, *P. grandiflora* Mann, *P. hexandra* Mann, *P. hirtella* Skottsb., *P. insularum* A. Gray, *P. loniceroides* DC., *P. pinnatinervia* Elm., *Randia cumingiana* Vid., *R. graeffii* Rein., *Sarcocephalus cordatus* Miq., *Straussia hillebrandii* Rock, *S. kaduana* (Cham. & Schl.) A. Gray, *S. mariniana* (Cham. & Schl.) A. Gray, *S. psychotrichoides* Heller, *Timonius polygamus* (Forst.) Rob., and *Wendlandia luzoniensis* DC.

The stem bark of *Coprosma arborea* Kirk, *C. tenuifolia* Cheesem., *C. cuneata* Hook. f., *C. pumila* Hook. f., *C. repens* Rich., *C. rhamnoides* A. Cunn., and *C. robusta* Raoul is practically devoid of anthraquinone colouring matters but sucrose has been isolated from extracts of the two first-mentioned species.

Isolation of Asperuloside.—(a) *From* C. tenuifolia. The bark was obtained from a tree growing at Papa Aroha, near Coromandel. We are indebted to Dr. H. H. Allan for its identification. No colour reactions typical of anthraquinones were given by the bark. The air-dried, ground bark was extracted with acetone in a Soxhlet apparatus for 56 hr. During the extraction crystalline material separated which recrystallised from methyl alcohol (charcoal) as hexagonal prisms, m. p. and mixed m. p. with sucrose, 184°. The filtered extract, on concentration, deposited colourless needles of asperuloside (2·9%) which, after repeated crystallisation from ethyl alcohol, separated in needles, m. p. 131—132° after marked shrinking at 126°, $[\alpha]_D^{25}$ −198·6° (*l*, 1; c, 1·44 in H_2O) (Found, on air-dried material: C, 50·2, 50·1; H, 5·3, 5·5; OMe, 0; *C*-Me, 4·0, 3·95. $C_{18}H_{24}O_{12}$ requires C, 50·0; H, 5·6; 1*C*-Me, 3·5. Found, on material dried at 110° over P_2O_5: C, 52·15; H, 5·3. $C_{18}H_{22}O_{11}$ requires C, 52·2; H, 5·3%. Loss on drying: 3·7%. $C_{18}H_{22}O_{11},H_2O$ requires 4·17%). Asperuloside is not reduced at the dropping-mercury electrode.

(b) *From* C. arborea. The bark was collected from trees growing at Titirangi and Manurewa. The air-dried, ground bark, which gave no colour reactions typical of anthraquinones, was fractionally extracted with ethyl acetate (Soxhlet) for 100 hr. The first extraction (10 hr.), after standing for 2 days, was decanted from extremely viscous material. The latter was triturated with alcohol, washed with hot acetone, and crystallised from methyl alcohol, giving sucrose (0·8%), m. p. and mixed m. p. 180°, $[\alpha]_D^{25}$ +66·7° in H_2O (Found: C, 42·2; H, 6·3. Calc. for $C_{12}H_{22}O_{11}$: C, 42·1; H, 6·4%). The decanted material, together with the further extractions, on concentration deposited asperuloside (0·6%), m. p. 131—132°, after repeated crystallisation from acetone.

(c) *From* C. robusta *and* C. repens. Both barks from trees growing in the Auckland district were practically colourless, gave no colour reactions with sodium hydroxide solution, and after continuous extraction with acetone afforded asperuloside, m. p. 131—132°, in yields of 1·2 and 1·7% respectively.

(d) *From* C. lucida. The air-dried, ground bark was extracted with ether for 5 hr. and then with ethyl acetate for 60 hr. The ethyl acetate was concentrated in stages, the first material separating being the colouring matters described in Part IV (*J.*, 1949, 1241). The final concentrate crystallised when seeded with asperuloside, and afforded pure material, m. p. 131·5°, in the usual way.

All samples of asperuloside obtained above showed no depression of m. p. on admixture.

Asperuloside is soluble in water, alcohols (methyl to pentyl), acetone, ethyl acetate, dioxan, pyridine, and glacial acetic acid and insoluble in ether, benzene, chloroform, and ligroin. An aqueous solution is neutral but becomes yellow and finally reddish-brown on treatment with sodium hydroxide, carbonate, or hydrogen carbonate solution (more slowly with the weaker alkalis).

The formation of glucose on acid hydrolysis of asperuloside (Juillet *et al.*, *loc. cit.*) has been confirmed by the preparation of glucosazone, m. p. and mixed m. p. 203—204° (decomp.).

Asperuloside Tetra-acetate.—This derivative, prepared by the action of acetic anhydride in boiling pyridine, separated from alcohol in colourless plates, m. p. 154°, undepressed by a sample kindly supplied by Dr. A. R. Trim [Found, on material dried at room temperature: C, 53·3, 53·4, 53·6; H, 5·8, 5·8, 5·2; Ac, 43·3, 39·8. $C_{18}H_{18}O_7(O{\cdot}CO{\cdot}CH_3)_4$ requires C, 53·6; H, 5·2; 5Ac, 36·9%]. The anomalous acetyl values will be discussed later.

Asperuloside Tribenzoate.—Asperuloside (300 mg.), benzoyl chloride (1 c.c.), and pyridine (3 c.c.) were boiled under reflux for ½ hr., cooled, and poured on ice (100 c.c.). The viscous red oil which separated was triturated with alcohol and, after repeated crystallisation from the same solvent, separated in colourless needles, m. p. 165—166° [Found, after drying at 100°: C, 63·5; H, 5·1. $C_{18}H_{19}O_8(O{\cdot}CO{\cdot}C_6H_5)_3,\frac{1}{2}H_2O$ requires C, 63·6; H, 4·9%).

The test for asperuloside was carried out by heating a few fragments of the stem-bark for preference or, where necessary in the case of herbaceous material, the whole stem, with *ca.* 1 c.c. of 2N-hydrochloric acid. In most cases the very characteristic bluish-green colour appears on

boiling. In a few cases, there was doubtful coloration but, on standing, the presence of asperuloside was confirmed by the formation of the black precipitate of asperuligenol. With herbaceous material some negative tests may not necessarily be due to the absence of asperuloside but to the small scale on which the experiment was performed. Most of the material was obtained from the Cheeseman Herbarium, Auckland Institute and Museum, and we are greatly indebted to Dr. R. C. Cooper for assistance on the botanical aspects.

We are indebted to the Chemical Society, the Australian and New Zealand Association for the Advancement of Science, and the Royal Society of New Zealand for grants, and to Dr. L. C. Hobbis for the collection of specimens of *C. ciliata, C. cuneata, and C. pumila* from the Campbell Islands, and one of us (G. A. N.) for a Duffus Lubecki Scholarship and a Research Fund Fellowship.

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Organic Oxidation Processes. Part II. The Reaction of Lead Tetra-acetate with Toluene and Related Compounds.*

By G. W. K. CAVILL and D. H. SOLOMON.

[Reprint Order No. 5449.]

The oxidation of toluene, of a series of *p*-substituted toluenes, and of ethylbenzene with lead tetra-acetate is described. The specific formation of benzyl acetates (i) is facilitated by electron-releasing and retarded by electron-attracting substituents, (ii) is independent of the solvent, and (iii) does not involve free benzyl or acetate radicals.

LEAD TETRA-ACETATE was first employed as an organic oxidant by Dimroth and Schweizer (*Ber.*, 1923, **56**, 1375) who showed that it replaced hydrogen of an active methyl or methylene system by an acetoxyl group. In particular, toluene was oxidised to benzyl acetate, and di- and tri-phenylmethane gave the corresponding arylmethyl acetates. We now report the reaction of lead tetra-acetate with various *para*-substituted toluenes and, for the first time, a systematic examination of the influence of substituents (OMe, Me, Bu^t, Br, and NO_2) is recorded for this oxidant (cf. Criegee, "Newer Methods of Preparative Organic Chemistry," Interscience Publ., New York, 1948, p. 6). In addition, these oxidations provide evidence on the mechanism of the reaction.

Dimroth and Schweizer (*loc. cit.*) obtained an 11% yield of benzyl acetate from toluene, using boiling acetic acid as solvent. Our oxidations have been carried out in acetic acid solution at 80°; reaction then proceeds at a satisfactory rate and decomposition of lead tetra-acetate is minimised. The yield of the *para*-substituted benzyl acetate increases (within experimental limits) with the increasing electron-releasing power of the substituent group: *p*-bromo- 5%, *p*-nitro-toluene 7%, toluene 25%, *p*-methyl- 47%, *p-tert.*-butyl- 55%, and *p*-methoxy-toluene 60%. Benzyl acetate and the *p*-methoxy-, *p*-methyl, and *p-tert.*-butyl derivatives were readily separated by fractionation under reduced pressure from the unchanged toluenes, which were recovered. The smaller proportional amounts of *p*-nitro- and *p*-bromo-benzyl acetate proved difficult to separate from the parent toluenes but saponification values gave the percentages of acetate listed above, and *p*-nitro- and *p*-bromo-benzyl alcohol were then isolated.

The synthetic possibilities of this oxidation process, in which toluenes yield solely benzyl acetates, merit attention. The overall reaction is:

$$p\text{-R}\cdot C_6H_4\cdot CH_3 + Pb(OAc)_4 \longrightarrow p\text{-R}\cdot C_6H_4\cdot CH_2\cdot OAc + Pb(OAc)_2 + AcOH$$

That parent hydrocarbon is recovered indicates that some of the lead tetra-acetate suffers decomposition in acetic acid, even at 80°. [The decomposition of lead tetra-acetate has

* Part I, *J.*, 1954, 2785.

been investigated recently by Kharasch, Friedlander, and Urry (*J. Org. Chem.*, 1951, **16**, 533) and by Mosher and Kehr (*J. Amer. Chem. Soc.*, 1953, **75**, 3172).]

We have previously observed (Barron, Cavill, Cole, Gilham, and Solomon, *Chem. and Ind.*, 1954, 76) that the solvent can markedly influence the course of the lead tetra-acetate oxidation; *e.g.*, *p*-cresol yields 2 : 2-diacetoxy-4-methyl*cyclo*hexadienone in acetic acid, but 2 : 2′-dihydroxy-5 : 5′-dimethyldiphenyl in benzene. Hence, in the present investigation, toluene and its *p*-methoxy- and *p*-nitro-derivative have also been oxidised in benzene, but only the benzyl acetate, and in the same yield, was obtained. Oxidation of toluene, in excess of substrate, yields benzyl acetate.

Oxidation of active methyl and methylene systems by lead tetra-acetate has been assumed to involve free-radical processes, especially as this oxidant is capable of yielding free acetate and methyl radicals (cf. Kharasch, Friedlander, and Urry, *J. Org. Chem.*, 1951, **16**, 533). Thus Dewar (" Electronic Theory of Organic Chemistry," Oxford Univ. Press, 1949, p. 277) proposed the following mechanism for the oxidation of toluene and similar compounds :

Initiation :

$$Pb(OAc)_4 \longrightarrow Pb(OAc)_2 + 2{}^*OAc$$

Propagation :

$$^*OAc + Ph{\cdot}CH_3 \longrightarrow AcOH + Ph{\cdot}CH_2{}^*$$

$$Ph{\cdot}CH_2{}^* + Pb(OAc)_4 \longrightarrow Ph{\cdot}CH_2{\cdot}OAc + {}^*OAc + Pb(OAc)_2$$

Termination :

$$Ph{\cdot}CH_2{}^* + {}^*OAc \longrightarrow Ph{\cdot}CH_2{\cdot}OAc$$

Oxidation of toluene, at 80°, may be initiated by an acetate radical from the decomposition of lead tetra-acetate (as above) or, alternatively, an initial dehydrogenation by the more reactive methyl radical (from the decomposition of the acetate radical) takes place (cf. Waters, " The Chemistry of Free Radicals," Oxford Univ. Press, 1946, p. 231), *i.e.* :

$$^*OAc \longrightarrow {}^*CH_3 + CO_2$$

and

$$^*CH_3 + Ph{\cdot}CH_3 \longrightarrow Ph{\cdot}CH_2{}^* + CH_4$$

In either case, propagation would then proceed by a chain mechanism involving free benzyl and acetate radicals. Finally, Dewar (*loc. cit.*) has indicated that only one termination reaction, *i.e.*, formation of benzyl acetate, should occur readily, and dimerisation of the mesomeric benzyl radicals to form dibenzyl would be relatively slow.

Whereas Kharasch *et al.* (*loc. cit.*) obtained a trace of succinic acid from the oxidative decomposition of boiling acetic acid with lead tetra-acetate, we have been unable to isolate any dimeric products from the oxidation of toluene or the more reactive *p*-methoxytoluene with this reagent. That we obtain only benzyl acetates, even on reaction in benzene solution (which solvent would favour dibenzyl formation, cf. Part I, *J.*, 1954, 2785), indicates the absence of free benzyl or *p*-methoxybenzyl radicals. Moreover, were acetate or methyl radicals (from the decomposition of acetate radicals) involved we would expect reaction in chloroform or carbon tetrachloride to show solvent interchange. For example, Wessely and Schinzel (*Monatsh.*, 1953, **84**, 425) isolated ααα-trichloro-β-(3 : 5-dimethyl-4 hydroxyphenyl)ethane after reaction of mesitol, in chloroform, with acetyl peroxide (which is well known to yield acetate and methyl radicals; cf. Kharasch and Gladstone, *J. Amer. Chem. Soc.*, 1943, **65**, 15). However, our reaction of *p*-methoxytoluene with lead tetra-acetate, in carbon tetrachloride, gave only *p*-methoxybenzyl acetate; no chlorinated derivative such as a trichloroethane, *p*-methoxybenzyl chloride, or hexachloroethane was detected.

The absence of solvent effects suggests that benzyl and acetate radicals are not involved in our lead tetra-acetate oxidations, and this is confirmed by a comparative reaction with acetyl peroxide. Toluene and *p*-methoxytoluene with acetyl peroxide in acetic acid readily yield dibenzyl and 4 : 4′-dimethoxydibenzyl respectively. Whether the dibenzyls result from a dehydrogenation of the toluene system by a methyl rather than an acetate

radical, does not influence the conclusion that this free-radical process differs vastly from the oxidations with lead tetra-acetate. Kharasch, McBay, and Urry (*J. Org. Chem.*, 1945, **10**, 401) have reported an analogous oxidation of ethylbenzene with acetyl peroxide, in excess of substrate, 2 : 3-diphenylbutane and higher polymeric products being formed. We have now shown that lead tetra-acetate readily converts ethylbenzene into the α-acetoxy-derivative, in excess of substrate or in acetic acid, no dimeric products being isolated.

Thus lead tetra-acetate oxidises the active methyl group of the toluene system by a process which (i) is more effective the greater the electron-releasing power of the *para*-substituent, (ii) is independent of the solvent, and (iii) does not involve free benzyl or acetate radicals. Probably the fundamental step is the formation, from the toluene and lead tetra-acetate, of a complex which breaks down to yield only the benzyl acetate, acetic acid, and lead acetate. Such a specific, though slow, reaction has obvious similarities with the glycol fission. (For recent discussions of the mechanism of glycol fission see Rigby, *J.*, 1950, 1907, and Cordner and Pausacker, *J.*, 1953, 102.)

Experimental

Oxidation of Toluene with Lead Tetra-acetate.—(*a*) Toluene (27·6 g.; freshly distilled over sodium) and lead tetra-acetate (133 g., prepared by method of Dimroth, Friedemann, and Kämmerer, *Ber.*, 1920, **53**, 481) in "AnalaR" acetic acid (120 ml.) were heated at 80° (oil-bath) until no positive test for the oxidant (starch–iodide) was obtained (54 hr.). After distillation of the acetic acid and unchanged toluene under reduced pressure, the residue was extracted with ether (3 × 50 ml.). Lead acetate remained. The ethereal solution was washed with water, sodium hydrogen carbonate solution, and water, then dried ($MgSO_4$). Removal of the solvent gave benzyl acetate (11·0 g., 25%) as a pale yellow oil, further purified by distillation, b. p. 222—223° (Found: C, 72·0; H, 6·75. Calc. for $C_9H_{10}O_2$: C, 72·0; H, 6·7%). Toluene (12·8 g.; b. p. 110°, n_D^{20} 1·4902) was recovered.

(*b*) Analogous oxidations of toluene in acetic acid–ether (equivalent solvent conditions to those employed for acetyl peroxide oxidation), in benzene, and in toluene gave benzyl acetate in yields of 21, 20, and 25% respectively.

No dibenzyl could be detected in any of the above reactions.

Oxidation of Toluene with Acetyl Peroxide.—Toluene (4·7 g.) in acetic acid (32 ml.) was added to acetyl peroxide (6·0 g.; Gambarjan, *Ber.*, 1909, **42**, 4003) in ether (150 ml.). The ether was distilled and the reaction mixture heated at 80° until no positive test for the oxidant (starch–iodide) was obtained (1 hr.). Excess of toluene and the acetic acid were removed by distillation, leaving a yellow oil (1·4 g.) which, on sublimation, yielded dibenzyl (0·2 g.). Further purification by chromatography from light petroleum on neutralised aluminium oxide, and resublimation, gave the compound as colourless plates, m. p. and mixed m. p. 50° (Found: C, 92·4; H, 7·9. Calc. for $C_{14}H_{14}$: C, 92·3; H, 7·7%). An unidentified oil remained.

Oxidation of Ethylbenzene with Lead Tetra-acetate.—(*a*) Ethylbenzene (10·6 g.; freshly distilled over sodium) and lead tetra-acetate (44·3 g.) in acetic acid (40 ml.) were heated at 80° until no positive test for the oxidant was obtained (16 hr.). The mixture, worked up as described for toluene, gave α-methylbenzyl acetate (5·2 g., 32%) as a colourless oil, b. p. 215—216° (Found: C, 73·3; H, 7·4. Calc. for $C_{10}H_{12}O_2$: C, 73·2; H, 7·4%). Ethylbenzene (4·6 g.; b. p. 135—137°, n_D^{20} 1·4956) was recovered.

(*b*) Similar oxidation of ethylbenzene (26·5 g.) with lead tetra-acetate (44·3 g.) in the absence of added solvent gave α-methylbenzyl acetate (10·3 g., 63% based on the lead tetra-acetate) as a colourless oil, b. p. 213—217° (Found: C, 73·3; H, 7·5%). Unchanged ethylbenzene (13·7 g.; b. p. 136°, n_D^{20} 1·4958) was recovered.

Oxidation of p-*Methoxytoluene with Lead Tetra-acetate.*—(*a*) *p*-Methoxytoluene (36·6 g.; Korner, *Jahresber. Fortschr. Chem.*, 1867, 682) and lead tetra-acetate (133 g.) in acetic acid (120 ml.) were heated at 80° until no positive test for the oxidant was obtained (3 hr.). The mixture, after distillation of acetic acid under reduced pressure, was worked up as described for toluene. The yellow oil (38·1 g.), so obtained, was fractionated to give *p*-methoxytoluene (5·7 g.; n_D^{19} 1·5122) and *p*-methoxybenzyl acetate (32·4 g., 60%; n_D^{20} 1·5118) as a colourless oil, b. p. 150°/23 mm. (Found: C, 66·7; H, 6·6%; sap. val., 306, 300. Calc. for $C_{10}H_{12}O_3$: C, 66·7; H, 6·7%; sap. val., 311).

(*b*) Similar oxidations of *p*-methoxytoluene in benzene, and in carbon tetrachloride, gave the *p*-methoxybenzyl acetate in yields of 51 and 56% respectively. The unchanged *p*-methoxytoluene was recovered in each case and no 4 : 4′-dimethoxydibenzyl could be detected. The product from oxidation in carbon tetrachloride gave no test (Lassaigne's) for halogen.

Oxidation of p-*Methoxytoluene with Acetyl Peroxide.*—*p*-Methoxytoluene (6·0 g.) in acetic acid (37 ml.) was added to acetyl peroxide (6·0 g.) in ether (150 ml.). The mixture, treated as for toluene, gave a semisolid residue (2·2 g.). Distillation of this product yielded *p*-methoxytoluene (1·3 g.; n_D^{19} 1·5140; sap. val., 0) and a residual solid (0·8 g.), which after purification by chromatography gave 4 : 4′-dimethoxydibenzyl, finally isolated as colourless prisms, m. p. 124°, from ethanol (Found: C, 79·1; H, 7·7. Calc. for $C_{16}H_{18}O_2$: C, 79·3; H, 7·5%). Freund and Reitz (*Ber.*, 1906, **39**, 2219) record m. p. 125°.

Oxidation of p-*Xylene and* p-tert.-*Butyltoluene.*—(*a*) *p*-Xylene (10·6 g., freshly distilled over sodium) and lead tetra-acetate (44·3 g.) in acetic acid (40 ml.) were heated at 80° (30 hr.). The mixture, when treated as for toluene, gave *p*-methylbenzyl acetate (7·5 g., 47%), b. p. 227—230° (Found: C, 73·6; H, 7·4%; sap. val., 337. Calc. for $C_{10}H_{12}O_2$: C, 73·2; H, 7·4%; sap. val., 342), and *p*-xylene (4·3 g.; b. p. 138°, n_D^{20} 1·4955).

(*b*) Similar oxidation of *p-tert.*-butyltoluene (14·8 g.; Bialobrzeski, *Ber.*, 1897, **30**, 1773) with lead tetra-acetate (44·3 g.) in acetic acid (40 ml.) gave *p-tert.*-butyltoluene (5·2 g.; b. p. 64°/18 mm., n_D^{17} 1·4943) and *p-tert.*-butylbenzyl acetate (11·3 g., 55%), b. p. 142°/15 mm. (Found: C, 75·5; H, 8·7%; sap. val., 280. Calc. for $C_{13}H_{18}O_2$: C, 75·7; H, 8·8%; sap. val., 272).

Oxidation of p-*Nitro- and* p-*Bromo-toluene with Lead Tetra-acetate.*—(*a*) *p*-Nitrotoluene (27·4 g., recrystallised from aqueous alcohol) and lead tetra-acetate (88·6 g.) in acetic acid (80 ml.) were heated at 80° (12 hr.). The mixture, worked up as described for *p*-methoxytoluene, but with chloroform for extraction, gave a yellow semisolid mass (28·7 g.) which contained mainly *p*-nitrotoluene and some *p*-nitrobenzyl acetate (7%, estimated by sap. value). The saponified mixture was then chromatographed on neutralised aluminium oxide; elution with light petroleum yielded *p*-nitrotoluene (23·4 g.; m. p. and mixed m. p. 50—51°), and with methanol–chloroform (10 : 90) gave *p*-nitrobenzyl alcohol (1·4 g.), finally isolated as yellow needles, m. p. and mixed m. p. 91—92° (from light petroleum).

(*b*) Similarly, *p*-nitrotoluene (13·7 g.) with lead tetra-acetate (44·3 g.) in benzene (110 hr., test for oxidant still positive) yielded recovered *p*-nitrotoluene (10·0 g.), m. p. and mixed m. p. 51°, and *p*-nitrobenzyl alcohol (0·3 g.), m. p. and mixed m. p. 91°. 4 : 4′-Dinitrodibenzyl was not detected.

(*c*) *p*-Bromotoluene (17·1 g., purified by distillation over sodium) with lead tetra-acetate (44·3 g.) in acetic acid (40 ml.) was heated at 80° for 110 hr., the test for oxidant being still positive. The mixture, worked up as described in (*a*) but with ether for extraction, gave recovered *p*-bromotoluene (10·0 g.), m. p. and mixed m. p. 26—27°, and *p*-bromobenzyl alcohol (0·5 g.), pale yellow needles, m. p. and mixed m. p. 76—77° (from light petroleum). The sap. value, before chromatography, indicated 5% of *p*-bromobenzyl acetate.

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The Form of Catalyst Poisoning Curves.

By E. B. Maxted and G. T. Ball.

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The form of the catalyst poisoning curve representing the variation of the activity of a progressively poisoned platinum catalyst with the poison content of a hydrogenation system, has been remeasured. Additional precision has been possible by the use of a specially stabilised stock of platinum black and by taking into account the mobile nature of the competitive adsorption of the poison and of the unsaturated substance used in the hydrogenation tests. The poisoning curve is initially very nearly linear but is slightly curved even at early stages of poisoning, although formerly thought to be strictly linear there.

A further study of the form of the curve expressing the relation between the activity of a hydrogenation catalyst and the poison content of the system hydrogenated was suggested by the availability of two ways recently developed for increasing the precision of the measurements involved. The first consists in a simple and effective method for stabilising the grain size of catalysts such as platinum black when these are used in liquid-phase hydrogenation. The second lies in the rather unexpectedly easy reversibility of the adsorption of many types even of strong poisons, and of the mobility of the competitive adsorption between the poison and the unsaturated substance for the occupation of catalyst surface (Maxted and Ball, *J.*, 1952, 4284; 1953, 3153; 1954, 2778). As a result of this mobility, an adsorbed poison can be readily displaced by desorption, assisted by mass action, on applying a relatively large concentration of an unsaturated substance; or conversely, in the course of the hydrogenation of a system containing both a poison and an unsaturated species, additional poison, over and above that originally adsorbed, will move continuously from the free phase on to the catalyst as the concentration of the unsaturated substance in the system is decreased as a result of its hydrogenation to a saturated and therefore weakly adsorbed form.

By determining the individual points on the poisoning curve under conditions which are certainly more precise than those previously available, it has been found that, although initially the activity varies very nearly linearly with the poison content, yet this more exact study shows the graph to be slightly curved from its inception and to increase progressively in curvature; as the poison content of the system is still further increased, there is a region of rather sudden inflexion away from the activity axis. This is of interest since the initial, quasi-linear portion of the graph was formerly thought to be strictly linear (Maxted, *J.*, 1921, **119**, 225, and later papers).

Experimental

The reaction used for assessing the activity, at various stages of poisoning, of a known weight of platinum catalyst, weighed out as required from a stabilised stock, involved the liquid-phase hydrogenation of *cyclo*hexene or crotonic acid. The activity tests were carried out in a thermostat at 30° in conjunction with a hydrogenation shaker operated under standardised conditions. This shaker, which has been developed over a number of years in order to obtain a high degree of reproducibility, actuates a small, vertically shaken hydrogenation pipette at a rate the constancy of which can be checked continuously throughout each run. The absorption of hydrogen is read off directly on a gas-burette system. Methyl sulphide was taken as the poison; and the usual hydrogenation charge consisted of 1 c.c. of *cyclo*hexene (or 0·01 mole of crotonic acid), 9 c.c. of acetic acid containing a varied weight of the poison, and either 0·025 or 0·05 g. of platinum.

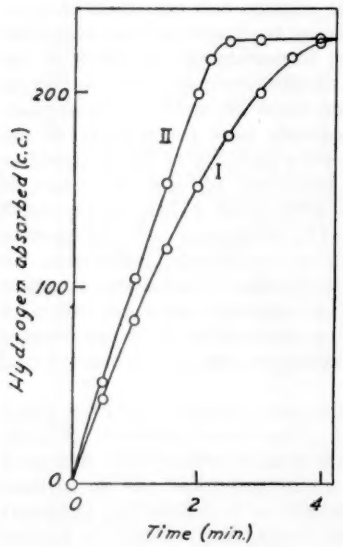
Stabilisation of the Catalyst.—Platinum black, made from chloroplatinic acid by alkaline formate reduction, is liable to change appreciably in grain size and consequently in surface area during its use for catalytic hydrogenation, with corresponding activity variations due to partial peptisation or coagulation rather than to poisoning.

It has been found that platinum black can be stabilised and activated if the usual exhaustive washing by decantation is supplemented by shaking the platinum rather vigorously in a mechanical shaker with successive changes of hot distilled water containing 5% of acetic acid,

the catalyst being separated from the supernatant liquid, at each change, by centrifuging. After this treatment, the platinum was dried at 100°, lightly ground in an agate mortar to remove lumps, and stored. From this stock, charges were weighed out as required; they gave closely reproducible results, together with a close adherence to zero-order reaction kinetics in an unpoisoned system. The improved kinetics and the general activation effect induced by this treatment are illustrated, for an unpoisoned system, in Fig. 1. In this, Curve I shows the course of hydrogenation obtained with a stock of platinum which had been exhaustively washed by decantation only. Curve II was given by the same platinum stock after it had been subjected to the stabilising treatment. Both systems consisted of *cyclo*hexene, acetic acid, and platinum (0·025 g.), as above.

The stabilising effect of the new treatment may lie in a more thorough leaching of alkali salts (from the alkali formate reduction) out of the internal pores of the catalyst grains than can be obtained even by long-term washing by ordinary decantation, since the presence of such salts is known to cause instability and especially coagulation during the use of the catalyst; further, this extension of the available internal surface within the grains would account for the increase in activity which is also obtained. It may be noted that Feulgen (*Ber.*, 1921, **54**, 360) has used intermittent violent shaking to prevent the passage of platinum into a difficultly washable, highly dispersed form during ordinary washing by decantation.

FIG. 1.



Kinetic Form of Individual Hydrogenation Runs.—In the absence of a poison, the linear zero-order form of the reaction path allows a direct and accurate evaluation of the reaction velocity. If a poison is present, two superimposed effects will cause curvature in the ordinary graph of total hydrogen absorption against time. First, poison will move from the free phase on to the catalyst as the concentration of the unsaturated substance decreases by reason of its hydrogenation. Secondly, unless the poisoned hydrogenation system has been allowed to remain in contact with the catalyst for the very long time (see *J.*, 1954, 2778) required for the attainment of equilibrium before starting the hydrogenation run, the adsorption will still be incomplete, and some poison will also move on to the catalyst by the continuation of simple adsorption during the test. The incidence of the latter process, which is additional to adsorption of poison caused by the gradual disappearance of the unsaturated component from the system, can be reduced to a negligibly low amount for the short period of the test by allowing the system to remain in the thermostat for about 1 hr. before starting the test. Even if this adsorption of poison were allowed to proceed until a very low rate had been reached before the hydrogenation is started, it is doubtful whether, at any rate in fast runs, the shift in the adsorbed poison content of the catalyst would keep pace with the changing conditions induced by the disappearance of the unsaturated component. In view of this probable time lag and of the lack at present of sufficient data to separate the two factors inducing a curved reaction path in the presence of a poison, curvature during a run has to be dealt with experimentally by reducing this complicating factor to a minimum.

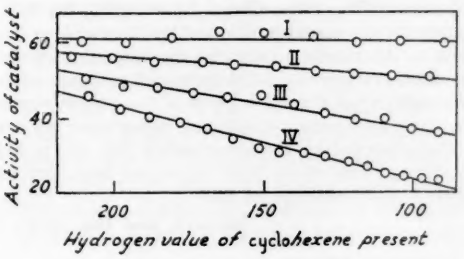
The progressive fall in the reaction rate as hydrogenation proceeds in poisoned systems is most clearly seen if—instead of plotting the total hydrogen absorption against time—the instantaneous hydrogenation velocities are plotted against the residual concentrations of the unsaturated component, which for convenience can be expressed in terms of its hydrogen value, *i.e.*, as the number of c.c. of hydrogen required for its saturation. This is illustrated in Fig. 2 for a series of hydrogenation runs with various concentrations of poison. The system in each case was that mentioned on p. 3947, together with the amount of dimethyl sulphide indicated for the individual graphs. The unpoisoned run (I) is, of course, unaffected by any " moving-on " effect and is of zero-order, with a uniform hydrogenation rate throughout. In each of the poisoned runs, on the other hand, the activity of the catalyst, expressed in the Figure as the instantaneous hydrogenation velocity, in c.c. of hydrogen per min., falls continuously and

approximately linearly with the decrease in the concentration of the unsaturated substance, which effect is evidently the major factor in causing curvature in the ordinary hydrogenation graphs.

A further set of similar graphs was obtained by using 10^{-2} mole of crotonic acid as the unsaturated substance, in place of 1 c.c. of *cyclo*hexene, but in an otherwise similar hydrogenation system. In this case, the departure from zero-order kinetics in the presence of the poison was less marked. This was to be expected, since crotonic acid is known from other work to be less strongly adsorbed than *cyclo*hexene; and, consequently, its progressive disappearance as the hydrogenation proceeds should have a smaller effect on the moving of additional poison on to the catalytic surface during a hydrogenation run.

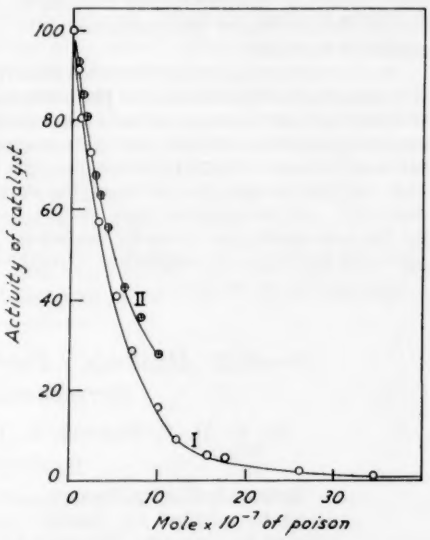
Form of the Poisoning Curve.—This curve, which is based on a series of hydrogenation runs in which the poison content of the system is varied from run to run, gives the influence of the total poison content on the initial activity of the catalyst, before additional poison has begun to move on to the catalyst as a result of the progressive disappearance of the unsaturated

FIG. 2.



Concentration of dimethyl sulphide:
I, O;
II, $0{\cdot}4 \times 10^{-6}$M;
III, $1{\cdot}0 \times 10^{-6}$M;
IV, $1{\cdot}5 \times 10^{-6}$M.

FIG. 3.



substance. In order to reduce the incidence of this moving-on factor to a lower value than that observed with *cyclo*hexene, crotonic acid was used as the unsaturated substance. The system taken for Curve I of Fig. 3 consisted of 10 c.c. of a N-solution of crotonic acid in acetic acid, containing in the individual runs the various amounts of dimethyl sulphide shown in the abscissæ, and 0·025 g. of stabilised platinum catalyst. The poisoned system was allowed to remain in the hydrogenation pipette in contact with the platinum for about an hour in the thermostat at 30° before the admission of hydrogen and the starting of the hydrogenation shaker. The activities are expressed in the Figure as percentages of the original unpoisoned activity of the catalyst.

The evaluation of the initial activity of the platinum in the run carried out without poison presents no difficulty since, in this case, the hydrogenation velocity is substantially constant throughout the run; but in the poisoned runs, in which the moving-on effect causes curvature in the hydrogenation graph (namely, a progressive fall in the instantaneous hydrogenation rate as the run proceeds), the initial velocity has to be obtained by extrapolating the instantaneous rate at various times back to that at zero time, or by the equivalent method of extrapolating graphs of the type of Fig. 2 back to the hydrogen value corresponding to the amount of unsaturated substance present at the start of the run.

It will be seen from Fig. 3 that, although the variation of the activity with the poison content is at first not far from linear, the graph is never strictly linear and corresponds to a continuous curve in which the very slight initial curvature increases progressively and, at a later stage, undergoes a rather sharp inflexion away from the activity axis, after which it falls far less

steeply with still further increased poison concentrations. Curve II in Fig. 3 summarises a further, shorter series of measurements, made with 0·05 g. of a different and less active specimen of stabilised platinum, this series of tests being carried out mainly to confirm the existence of curvature in the initial portion of the poisoning graph.

Curves of the above nature, in which the inhibitive effect measured by the fall in activity is plotted against the total poison introduced, are called effective toxicity curves to distinguish them from those in which the observed inhibition is plotted against the amount of poison actually adsorbed on the catalyst, which are called true poisoning curves. It will be obvious, from the mobility of the competition between a poison and an unsaturated substance for the occupation of catalyst surface, that the accurate determination of true toxicity curves is more difficult than that of effective toxicity curves, since the assessment of instantaneous adsorbed poison concentrations involves dealing with a far more complex equilibrium than was previously supposed and would involve a knowledge both of the respective adsorption equilibrium constants and especially of the attendant rate constants which govern the adsorption and desorption of the particular poison and unsaturated substance used. All these are at present not known. For this reason, it seems certain that the structure of true, as distinct from effective, poisoning curves should receive renewed attention; and it is hoped to deal with this subject in a subsequent paper.

In this connection it may be noted that Kubokawa (*Rev. Phys. Chem. Japan*, **1937**, **11**, 202), who examined the poisoning of a platinum catalyst for the decomposition of hydrogen peroxide, obtained a linear relation between the logarithm of the reaction rate and the logarithm of the amount of poison adsorbed; but this adsorbed concentration was not determined with consideration of the poison mobility factors (*i.e.*, the reversibility of the adsorption of the poison alone, and any interference by virtue of the competitive and poison-displacing adsorption of the reactant). A similar logarithmic relation was also observed by the same author (*loc. cit.*, p. 82) for the non-specific and probably mechanical covering effect of the layer of carbon deposited on platinum during the decomposition of methane on a platinum wire at 1200°.

UNIVERSITY OF BRISTOL. [*Received, June 11th*, 1954.]

Steroidal Alkaloids. Part III. The Constitution and Stereochemistry of Cevine.*

By D. H. R. BARTON, C. J. W. BROOKS, and P. DE MAYO.

[Reprint Order No. 5524.]

Methanolysis of cevine orthoacetate triacetate affords cevine orthoacetate diacetate, oxidised by chromic acid to a ketone. A similar oxidation is effected on cevadine orthoacetate acetate. These experiments show that cevine contains no primary hydroxyl group.

The constitutions of various acetylated cevadine derivatives are discussed and the possible presence of an enol acetate grouping is considered.

Catalytic hydrogenation of cevine orthoacetate triacetate affords cevine " dihydro-orthoacetate " triacetate in which the presence of an ethylenedioxy-group has been detected. This confirms the presence of an orthoacetate grouping in the precursor.

Reduction of cevine orthoacetate triacetate with lithium and liquid ammonia furnishes a dihydrocevine orthoacetate, the triacetate of which is stable to chromic acid. This and other evidence confirms that the terminus of the oxide ring in cevine is derived from a tertiary hydroxyl group.

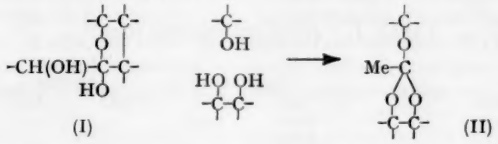
Evidence is presented that the orthoacetate system of cevadine orthoacetate diacetate and related compounds is attached both α and β with respect to the 16-hydroxyl group.

Treatment of dihydrocevine orthoacetate with dilute sulphuric acid affords an isomeric orthoacetate. The bearing of this and other observations on the stereochemistry of cevine is briefly discussed.

IN Parts I and II of this series * the oxygenated functional groups of the steroidal alkamine cevine, $C_{27}H_{43}O_8N$, were shown to be as follows : three oxygen atoms bound up in a masked

* Part I and II, *J.*, 1953, 424; 1954, 2137.

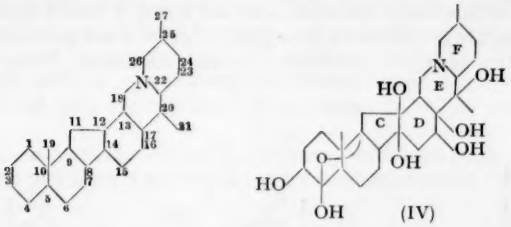
secondary α-ketol system (I); two more present as a ditertiary α-glycol system related in space to a third tertiary hydroxyl in such a way as to explain ready formation of an ortho-acetate (II); the remaining two oxygen atoms present one as a primary or secondary hydroxyl group and one as a tertiary hydroxyl group. We commence the present paper by clarifying the final obscurity in the nature of the functional groups.



(I) (II)

Methanolysis of cevine orthoacetate triacetate, which is known to be base-catalysed (see Rosenfelder, *J.*, 1954, 2638), removed one acetate residue preferentially, affording cevine orthoacetate diacetate. The ease of this reaction implies that the acetate residue removed was attached to a primary or a secondary hydroxyl group. That the latter is correct was demonstrated by titrimetric oxidation of cevine orthoacetate diacetate to a ketone. A primary hydroxyl group cannot, therefore, be present in cevine.

Whilst the work on the functional groups summarised in this paper and in Parts I and II was in hand parallel studies on the more vigorous degradation of the cevine molecule were in progress in other laboratories. On the basis of dehydrogenation evidence Jacobs and Pelletier proposed (*J. Org. Chem.*, 1953, **18**, 765) and supported (*J. Amer. Chem. Soc.*, 1954, **76**, 2028) the fundamental skeleton (III) for cevine and related alkaloids. In the laboratories at Zürich and at Harvard elegant oxidative degradational studies of the cevine molecule have been pursued, of the progress of which we have, from time to time, been informed. Summing the evidence available, both experimental and interpretative, made structure (IV) very plausible for cevine. In collaboration with Dr. O. Jeger and Professor



(III) (IV)

V. Prelog of Zürich and with Professor R. B. Woodward of Harvard, the arguments in favour of this structure have recently been summarised [Barton, Jeger, Prelog, Woodward (and their respective collaborators), *Experientia*, 1954, **10**, 81]. We express here our cordial appreciation of the friendly international exchange of facts and theories which eventually made possible this joint paper. It is not our intention to repeat now any of the closely woven skein of logic used in the derivation of structure (IV) and we content ourselves with summarising the relevant, hitherto unpublished experiments, carried out at Birkbeck College, which may be adduced as support for the formula.

Treatment of cevadine (V; R = angeloyloxy) with acetic anhydride–perchloric acid affords cevadine orthoacetate diacetate (Stoll and Seebeck, *Helv. Chim. Acta*, 1952, **35**, 1942; Kupchan, Lavie, Deliwala, and Andoh, *J. Amer. Chem. Soc.*, 1953, **75**, 5519). This can be selectively methanolysed to cevadine orthoacetate acetate and we find that titrimetric chromic acid oxidation of the monoacetate affords a ketone stable to further attempted oxidation. This confirms the absence of a primary hydroxyl group in cevine (cf. above). Careful alkaline hydrolysis (Stoll and Seebeck, *loc. cit.*) of cevadine orthoacetate acetate affords cevadine orthoacetate.

The infra-red spectra (all in CS_2) of this series of compounds (see Table 1) revealed that their structural basis might be more complicated than indicated by the names given above.

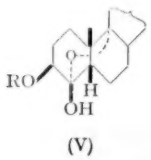
Thus all the compounds retaining the acetate grouping at $C_{(4)}$ showed marked shifts of the bands for the 4-acetate and the 4-angelate group relative to the expected positions. It has been suggested to us by Dr. O. Jeger (personal communication) that the simplest interpretation of these shifts is that the 4-acetates are really enol-acetates. Thus cevadine orthoacetate diacetate is possibly to be formulated as cevadine orthoacetate enol-acetate acetate

TABLE 1. *Infra-red maxima* (cm.$^{-1}$).

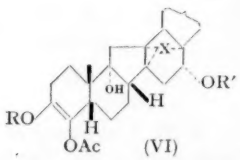
Compound	Angelate C:O	Angelate C:C	(?) Enol angelate C:O	(?) Enol angelate C:C	Acetate C:O	(?) Enol acetate C:O
Cevadine	1705 1232	1640	—	—	—	—
Cevadine orthoacetate diacetate	—	—	1722 1230	1640	1738 1244	1764 1216
Cevadine orthoacetate acetate	—	—	1725 1232	1644	—	1765 1216
Dihydrocevadine orthoacetate acetate	—	—	—	—	—	1762 1222
Cevadine orthoacetate	1708 1230	1638	—	—	—	—
Ketone (XII; R = angeloyloxy) from cevadine orthoacetate acetate	—	—	1723 1238	1640	—	1760 1218

(VI; R = angeloyloxy, R′ = Ac), and cevadine orthoacetate acetate as cevadine orthoacetate enol-acetate (VI; R = angeloyloxy, R′ = H). In cevadine orthoacetate the carbonyl frequency is again normal, which would indicate re-closure to the original masked α-ketol system as in (VII; R = angeloyloxy).

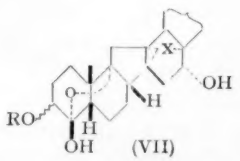
In an endeavour to confirm the postulated enol-acetate structures, cevadine orthoacetate was acetylated by pyridine–acetic anhydride to give a new compound which we regard as acetylated at $C_{(16)}$. Further acetylation with acetic anhydride–perchloric acid afforded the known cevadine orthoacetate diacetate, and not a ring-A closed isomer. Also treatment of cevadine orthoacetate acetate with N-sulphuric acid did not provoke isomerisation to a new orthoacetate system as might have been expected (see below) if a free 9-hydroxyl group had been available.



(V)

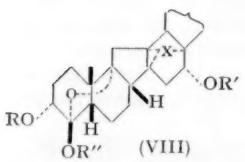


(VI)

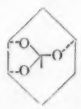


(VII)

The ring containing X is to be understood as being the grouping (*A*).



(VIII)

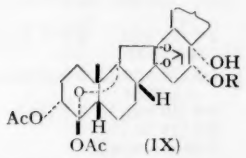


(*A*)

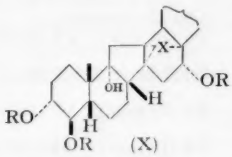
Catalytic hydrogenation of the perchlorate of cevine orthoacetate triacetate (VIII; R = R′ = R″ = Ac) in acetic acid with a platinum catalyst furnished a cevine "dihydro-orthoacetate" triacetate which we formulate as the ethylenedioxy-compound (IX; R = Ac) on the basis of the following evidence. Acetyl determination showed the presence of only three acetic acid residues; acid hydrolysis afforded acetaldehyde, isolated as the 2 : 4-dinitrophenylhydrazone; oxidation with chromic acid gave back cevine orthoacetate triacetate. Partial methanolysis furnished cevine "dihydro-orthoacetate" diacetate (IX; R = H). These experiments may be taken as confirmatory for the formulation of "an-

hydrocevine " as cevine orthoacetate (Part II, *loc. cit.*; see also Stoll and Seebeck, *Helv. Chim. Acta*, 1954, **37**, 824).

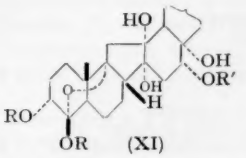
One of the features of cevine chemistry about which it was difficult to furnish a direct proof in Parts I and II was the terminus of the oxide ring (now secured at $C_{(9)}$, see above). We originally concluded (see Part II) that this affords a tertiary hydroxyl group since cevagenin orthoacetate diacetate is stable to chromic acid. Although the interpretation of this experiment is subject to qualification (see below) the conclusion reached is correct and is confirmed as follows. Reduction of cevine orthoacetate triacetate (VIII; R = R′ = R″ = Ac) with lithium and liquid ammonia gave dihydrocevine orthoacetate (X; R = H), which readily afforded a triacetate (X; R = Ac) on acetylation with pyridine and acetic



(IX)



(X)



(XI)

anhydride. This triacetate was stable to chromic acid and therefore cannot contain an unacetylated (C_7) secondary hydroxyl group. The assigned β-configuration at $C_{(4)}$ in dihydrocevine orthoacetate triacetate (X; R = Ac) is based on the presumed carbanionic mechanism of reduction (see Barton and Robinson, *J.*, 1954, 3045).

A structural feature of some uncertainty in the cevine formula (IV) of Barton, Jeger, Prelog, and Woodward (*loc. cit.*) is the attachment of a tertiary hydroxyl at $C_{(17)}$ rather than at $C_{(13)}$. We are now able to provide firm evidence as to the correctness of the formulation of ring D in (IV). Selective methanolysis of cevine 3 : 4 : 16-triacetate (XI; R = R′ = Ac) gave cevine 3 : 4-diacetate (XI; R = Ac, R′ = H). Chromic acid oxidation then furnished a ketone which showed an infra-red maximum at 1702 cm.$^{-1}$ (6-ring ketone) in agreement with the assigned constitution. When, however, cevine orthoacetate diacetate (VIII; R = R″ = Ac, R′ = H) (see above) was similarly oxidised the derived ketone was shown by quantitative infra-red spectroscopy to have the carbonyl band displaced to 1730 cm.$^{-1}$. Such a displacement could only be explained by a change in α- [as in (VIII)], not β-, substitution.

In agreement with these structures stand experiments with lead tetra-acetate and with periodic acid summarised in Tables 2 and 3. In order to conserve space we do not present

TABLE 2. *Lead tetra-acetate oxidations.*

Compound oxidised	Mols. of oxidant added	Mols. of oxidant consumed at various times
Cevadine	3·0	1·0 (10 min.); 1·5 (5 hr.); 3·0 (16 hr.)
Cevadine orthoacetate	3·0	0·0 (2 hr.); 0·0 (16 hr.)
Cevadine orthoacetate acetate	3·0	0·0 (2 hr.); 0·0 (16 hr.)
Ketone (XII; R = angeloyloxy)	3·4	0·0 (2 hr.); 0·0 (16 hr.)
Cevine triacetate (see Part II)	4·0	0·95 (10 min.); 0·95 (18 hr.)
Cevine 3 : 4-diacetate	3·0	0·95 (10 min.); 1·8 (5 hr.); 3·0 (16 hr.)
Cevine 3 : 16-diacetate	3·3	0·97 (10 min.); 2·5 (4 days)
Cevine 16-acetate perchlorate (see Exptl.)	3·2	2·0 (10 min.); 2·0 (1 hr.); 2·9 (4 days)
Ketone from cevine 3 : 4-diacetate	3·4	1·5 (10 min.); 2·4 (3 hr.); 3·4 (20 hr.)

a detailed discussion of the results, but trust that the interpretation will be clear from the formulæ given. We would however direct attention to one especially striking set of results. Cevine 3 : 4 : 16-triacetate (XI; R = R′ = Ac) consumes only one mol. of lead tetra-acetate even on long treatment, but the derived 3 : 4-diacetate (XI; R = Ac, R′ = H) takes up nearly two mols. in 5 hours in agreement with the view that partial methanolysis of the triacetate reveals a cleavable glycol system (at position 16 : 17). The ketone from oxidation of cevine 3 : 4-diacetate behaved similarly.

A proof that one end of the orthoacetate system in cevine derivatives was placed β with

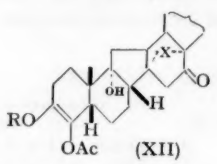
respect to the 16-hydroxyl group was obtained as follows The ketone (XII; R = angeloyloxy) obtained (see above) by oxidation of cevadine orthoacetate acetate (VI; R = angeloyloxy, R′ = H) was sensitive to base. On treatment with aqueous-methanolic sodium hydroxide at room temperature for a short period the ketone afforded an αβ-unsaturated ketone (XIII; R = angeloyloxy). The loss of the orthoacetate residue can only be explained by β-elimination (at $C_{(14)}$) as provided for by the above-cited formulæ.

TABLE 3. *Periodic acid oxidations.*

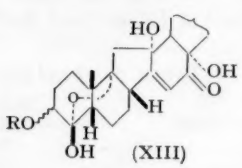
Compound oxidised	Mols. of oxidant added	Mols. of oxidant consumed at various times	
		No $NaHCO_3$.*	$NaHCO_3$ added.
Cevadine	2·0	0·90 (2—25 min.)	—
Cevine	4·5	2·0 (10 min.); 2·0 (24 hr.)	2·7 (15 min.); 3·5 (1 hr.); 4·5 (2 hr.)
Cevagenin	4·5	2·0 (1 hr.); 2·0 (2 hr.)	1·5 (15 min.); 2·5 (2 hr.); 4·5 (6 hr.)
Cevine triacetate	5·0	1·0 (10 min.); 1·0 (16 hr.)	0·9 (10 min.); 3·2 (16 hr.)
Cevine tetra-acetate	4·5	—	0·0 (16 hr.)
Dihydrocevine orthoacetate	4	0·9 (10 min.); 0·95 (45 min.)	1·03 (45 min.)
Unsaturated ketone (XIII; R = angeloyloxy)	4·5	0·0 (2—60 min.)	0·16 (10 min.); 0·7 (70 min.); 2·0 (4 hr.)

* As shown on p. 3958 periodic acid oxidations of cevine derivatives are very dependent on pH. With periodic acid itself little, if any, oxidation occurs until sodium hydrogen carbonate is added just before titration. These experiments therefore measure the "instantaneous" periodic acid consumption.

Catalytic hydrogenation gave the dihydro-derivative (XIII; R = α-methyl-*n*-butyryl) showing $\lambda_{max.}$ 238 mμ (ε 12,500) in agreement with the assigned structure. The latter compound was also obtained by subjecting the ketone from dihydrocevadine orthoacetate acetate (XII; R = α-methyl-*n*-butyryl) to mild treatment with alkali. In the infra-red, the ketone (XIII; R = angeloyloxy) showed bands (in $CHBr_3$) at 1700 and 1240 (αβ-unsaturated ester grouping) and at 1672 $cm.^{-1}$ (αβ-unsaturated ketone), whilst its dihydro-derivative showed bands (in $CHBr_3$) at 1720 and 1260 (ester grouping) and at 1670 $cm.^{-1}$ (αβ-unsaturated ketone), both bands being of such an intensity as to correspond with only one carbonyl group. The infra-red data confirm that no extra ketonic grouping is produced in the genesis of these αβ-unsaturated ketones.



(XII)



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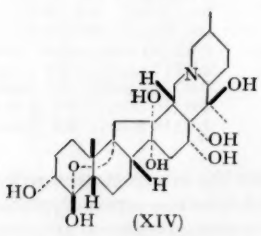
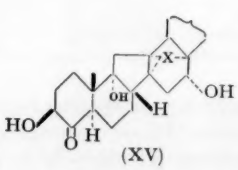


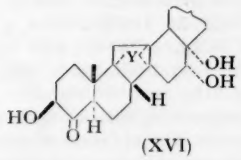
(XIV)



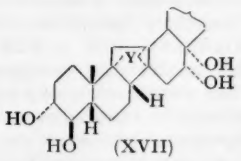
(XV)

The stereochemistry of cevine has already been discussed in outline by Barton, Jeger, Prelog, and Woodward (*loc. cit.*). The configurations at positions 3, 4, 5, 9, and 10 as in (XIV) may be taken as established and one may presume that the configuration at $C_{(8)}$ is β as in all other naturally occurring steroids. The α-configurations at positions 12, 14, and 17

are demonstrated by the following evidence. Stoll and Seebeck (*Helv. Chim. Acta*, 1952, **35**, 1942) reported that alkaline treatment of cevadine orthoacetate acetate afforded a cevagenin orthoacetate (amorphous, $[\alpha]_D$ +34° in EtOH), which would now be formulated (see Barton, Jeger, Prelog, and Woodward, *loc. cit.*) as (XV). Stoll and Seebeck later (*Helv. Chim. Acta.*, 1954, **37**, 824) stated that a repetition of essentially the same reaction conditions gave a crystalline cevagenin orthoacetate (m. p. 184—190°, $[\alpha]_D$ − 39° in EtOH). Both preparations of " cevagenin orthoacetate " gave crystalline cevagenin orthoacetate diacetate on acetylation. It was suggested to us by Dr. S. M. Kupchan (personal communication, *J. Amer. Chem. Soc.*, in the press) that the orthoacetate system of cevagenin orthoacetate, which is produced under mild acetylation conditions, might be in a different position from that which it occupies in cevine orthoacetate, which is obtained under strongly acid-catalysed conditions. According to Kupchan (*loc. cit.*) cevagenin orthoacetate is now to be formulated as (XVI). Treatment of dihydrocevine orthoacetate (X; R = H) with N-sulphuric acid or more simply, but more slowly, its dissolution in acetic acid, afforded a dihydrocevine *iso*orthoacetate (XVII) showing no carbonyl band in the infra-red but giving



(XVI)



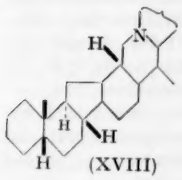
(XVII)

The ring containing Y is to be understood as being the grouping (*B*).

(*B*)

one mol. of acetic acid on acetyl determination. A repetition of the two groups of experiments reported by Stoll and Seebeck (*loc. cit.*) then revealed that it was extraction into N-sulphuric acid that permitted the rearrangement of the initially produced (amorphous and dextrorotatory) cevagenin 12 : 14 : 17-orthoacetate into the more stable 9 : 12 : 14-orthoacetate. The existence of these two series of orthoacetates proves that the 12-, 14-, and 17-hydroyl groups must be on the same (α-) side of the molecule as the 9-hydroxyl group. The same conclusion has also been drawn by Kupchan from his work referred to above. Also since hydroxyl groups at positions 7, 12, and 14 could not furnish an orthoacetate system (see models), the ether bridge of cevine could not terminate at the (secondary) 7-position, a conclusion already reached on other grounds (Barton, Jeger, Prelog, and Woodward, *loc. cit.*; see also above).

Cevine triacetate (see Table 3) is, after the consumption of one mol. of reagent, stable indefinitely to the action of lead tetra-acetate. It seems to us that this is only reasonable if the exposed diterciary α-glycol system at $C_{(17)}$ and $C_{(20)}$ is diaxial (cf. Criegee *et al.*, *Annalen*, 1933, **507**, 159; *Ber.*, 1940, **73**, 563), as already indicated. A diaxial arrangement for the 17 : 20-glycol system also fixes the configuration at $C_{(13)}$ (see models) in such a way as to give a *trans*-fusion of rings D and E.



(XVIII)

Finally we discuss the configuration at $C_{(16)}$ which was tentatively regarded as α by Barton, Jeger, Prelog, and Woodward (*loc. cit.*) on the basis of the ready methanolysis of compounds acetylated at this position. The faster cleavage of the 16 : 17-glycol system than of the 17 : 20-system (see Table 2) supports this view, but we are not able to offer conclusive evidence on this point of stereochemistry

In conclusion we advance nomenclature proposals which will probably be applicable also for zygadenine, germine, and protoverine. We suggest that the saturated compound represented by (XVIII) [for numbering see (III) above] should be called cevan. Cevine itself then becomes 4α : 9α-epoxycevan-3α : 4β : 12α : 14α : 16α : 17α : 20β-heptaol.

Experimental

For general experimental details see Part I (*J.*, 1953, 424). Unless specified to the contrary, rotations were determined in chloroform solution at room temperature, and light-absorption

maxima in ethanol (Unicam S.P.500 Spectrophotometer). Infra-red spectra were kindly determined by Messrs. Glaxo Laboratories Ltd. in carbon disulphide solution except as otherwise stated. Acetyl and other volatile-acid determinations were carried out according to Pregl's "Quantitative Organic Microanalysis" (by H. Roth; J. and A. Churchill Ltd., London, 1937).

Methanolysis of Cevine Orthoacetate Triacetate.—Cevine orthoacetate triacetate (2·0 g.) in methanol (100 ml.) was left at room temperature for 7 hr., after which water (20 ml.) was added and the solution left overnight. The solvent was removed under reduced pressure and the residue extracted with chloroform. Crystallisation from aqueous methanol gave *cevine orthoacetate diacetate* (600 mg.), m. p. 283—285°, $[\alpha]_D$ +104° (*c*, 2·14) (Found: C, 63·45; H, 7·7; Ac, 19·7, 19·9. $C_{33}H_{47}O_{10}N,\frac{1}{2}CH_3{\cdot}OH$ requires C, 63·5; H, 7·8; Ac, 20·35%).

Cevine orthoacetate diacetate (400 mg.; dried *in vacuo*) in "AnalaR" acetic acid (45 ml.) containing chromium trioxide (100 mg.) was left at room temperature. After 3 hr. two equivalents of oxidant had been consumed (unchanged on further standing). After working up as for the corresponding oxidation of cevadine orthoacetate acetate (see below), the product was crystallised from chloroform–methanol, to give the required *ketone* (200 mg.) as long needles, m. p. 275—276° (decomp.), $[\alpha]_D$ +98° (*c*, 1·20) (Found: C, 64·0; H, 7·3. $C_{33}H_{45}O_{10}N$ requires C, 64·35; H, 7·35%).

Chromic Acid Oxidation of Cevadine Orthoacetate Acetate.—Cevadine orthoacetate acetate, prepared according to Stoll and Seebeck's method (*Helv. Chim. Acta*, 1952, **35**, 1942), had m. p. 283—285° (decomp.), $[\alpha]_D$ +79° (*c*, 1·20 in EtOH), +72° (*c*, 1·33 in $CHCl_3$), +74° (*c*, 1·98 in $CHCl_3$) [Found: equiv. (determined by volatile acid produced on acid hydrolysis), 224. Calc. for $C_{36}H_{51}O_{10}N$ (one angelate and two acetate residues): equiv., 219].

(*a*) Cevadine orthoacetate acetate (200 mg.) was treated at room temperature with a solution of chromium trioxide (25 ml., 0·065N; five times the amount required for the oxidation of one secondary hydroxyl group) in "AnalaR" acetic acid containing 0·2% of water. Aliquot parts were titrated at intervals. After 2 hr. 95% of the theoretical amount of reagent had been consumed; there was no further uptake after another hour. The residual solution (21 ml.) was treated with a slight excess of aqueous sodium hydrogen sulphite at 10° and then with a slight excess of aqueous ammonia. Extraction with chloroform (6 × 30 ml.) and crystallisation from ethanol afforded the *ketone* (106 mg.) (XII; R = angeloyloxy) as fine needles m. p. 269—270° (decomp.), $[\alpha]_D$ +60° (*c*, 0·98), +58° (*c*, 1·24), +59° (*c*, 1·10) [Found: C, 65·65; H, 7·4; N, 2·6%; equiv. (by potentiometric titration), 663. $C_{36}H_{49}O_{10}N$ requires C, 65·95; H, 7·55; N, 2·15%; equiv., 656]. Treatment of this ketone (50 mg.) with chromium trioxide (twice the amount calc. for the oxidation of one secondary hydroxyl group) in "AnalaR" acetic acid (10 ml.) at room temperature for 4½ hr. resulted in no significant uptake of chromic acid (titration); the ketone was recovered unchanged (m. p., mixed m. p., and rotation).

(*b*) For larger-scale oxidations the following procedure was advantageous. Cevadine orthoacetate acetate (3·54 g.) in 95 : 5 (v/v) carbon tetrachloride–acetic acid (100 ml.) was treated with chromium trioxide solution (50 ml.; 0·66N) in 98·5% aqueous acetic acid for 1 hr. at room temperature, the reaction being controlled by titrations. After being worked up as outlined above, the crude product crystallised from ethanol to give the pure ketone (2·0 g., 59%).

Acetylation of Cevadine Orthoacetate.—Cevadine orthoacetate (Stoll and Seebeck, *Helv. Chim. Acta*, 1952, **35**, 1942) (230 mg.) in acetic anhydride (4 ml.) and pyridine (2 ml.) was heated on the steam-bath for 2 hr. Crystallisation of the product from ether–light petroleum (b. p. 40—60°) gave *cevadine orthoacetate 16-acetate*, m. p. 165—170°, $[\alpha]_D$ +83° (*c*, 1·09) [Found: C, 65·1, 65·45; H, 7·6, 6·8; N, 2·4%; equiv., 224. $C_{36}H_{51}O_{10}N$ requires C, 65·75; H, 7·8; N, 2·15%; equiv. (based on one orthoacetate, one acetate, and one angeloyloxy-residue), 219].

Cevadine orthoacetate 16-acetate (80 mg.) in acetic anhydride (4 ml.) was cooled to −60° and perchloric acid (70%; 0·4 ml.) added. The solution was left at −5° overnight. Crystallisation of the product from ether gave cevadine orthoacetate diacetate, identified by m. p., mixed m. p. and rotation.

Cevadine Triacetate.—Cevadine orthoacetate diacetate (200 mg.) in aqueous acetic acid (50%; 5 ml.) was left at room temperature for 2 hr., diluted with 500 ml. of water, and left for a further hour. Crystallisation of the product from aqueous acetone afforded *cevadine triacetate*, m. p. 265—266°, $[\alpha]_D$ +16° (*c*, 1·14) (Found: C, 62·8; H, 7·3; N, 1·85. $C_{38}H_{55}O_{12}N,\frac{1}{2}H_2O$ requires C, 62·8; H, 7·75; N, 1·9%). Heating of the triacetate (50 mg.) in "AnalaR" acetic acid (2 ml.) on the steam-bath for 10 min. gave back cevadine orthoacetate diacetate, identified by m. p., mixed, rotation, and crystal form.

Hydrogenation of Cevine Orthoacetate Triacetate Perchlorate.—The perchlorate (200 mg.) in "AnalaR" acetic acid (25 ml.) was hydrogenated overnight with a platinum catalyst. After

filtration most of the acetic acid was removed *in vacuo*, and the product was treated with water and adjusted to pH 9 with ammonia. Extraction with chloroform afforded *cevine " dihydro-orthoacetate " triacetate* as needles from chloroform–light petroleum (b. p. 60—80°), m. p. 270—273° (decomp.), $[\alpha]_D$ +58°, +60° (*c*, 0·88, 1·96 respectively in acetone), +59° (*c*, 1·37 in $CHCl_3$) (Found: C, 63·1; H, 7·8; Ac, 19·7, 20·1. $C_{35}H_{51}O_{11}N$ requires C, 63·5; H, 7·75; Ac, 19·5%). This compound was recovered unchanged on further attempted hydrogenation (with or without the addition of excess of perchloric acid) and was not acetylated by pyridine–acetic anhydride at steam-bath temperature. It was however also obtained by the hydrogenation of cevine ortho-acetate triacetate under the same conditions. As would be expected, cevine triacetate was unaffected on attempted hydrogenation as above. Cevine " dihydro-orthoacetate " triacetate reduced Fehling's solution at the same rate as did its progenitor.

The " dihydro-orthoacetate " (125 mg.) in " AnalaR " acetic acid (40 ml.) containing chromium trioxide (50 mg.) was left at room temperature. Aliquot parts were titrated and after 2 hr. the uptake of chromic acid ceased at the consumption of two equivalents. After 5 hr. the solution was worked up to give, on crystallisation from ether, cevine orthoacetate triacetate, identified by m. p., mixed m. p., rotation {$[\alpha]_D$ +121° (*c*, 1·03)}, analysis (Found: C, 63·45; H, 7·7; N, 2·6. Calc. for $C_{35}H_{49}O_{11}N$: C, 63·7; H, 7·5; N, 2·1%), and infra-red spectrum (identical in every detail with that of authentic material).

Detection of an Ethylidene Grouping in Cevine " Dihydro-orthoacetate " Triacetate.—The " dihydro-orthoacetate " (210 mg.) in methanol (7 ml.) was treated with 2 : 4-dinitrophenylhydrazine (70 mg.) in concentrated hydrochloric acid (1 ml.) on the steam-bath for 30 min. Dilution with water, extraction with chloroform, and filtration in 1 : 1 benzene–light petroleum (b. p. 40—60°) through alumina, and elution with benzene gave acetaldehyde 2 : 4-dinitrophenylhydrazone, identified by m. p., mixed m. p., absorption spectrum ($\lambda_{max.}$ 357 mμ, ε 21,100 in $CHCl_3$), and analysis (Found: C, 42·95; H, 4·1; N, 24·0. Calc. for $C_8H_8O_4N_4$: C, 42·85; H, 3·6; N, 25·0%).

Methanolysis of Cevine " Dihydro-orthoacetate " Triacetate.—The " dihydro-orthoacetate " (200 mg.) in methanol (20 ml.) was left at room temperature for 7 hr. Water (7 ml.) was added and the solution set aside overnight. The solvent was removed *in vacuo* and the crystalline precipitate was collected. Recrystallisation from aqueous methanol gave prisms of *cevine " dihydro-orthoacetate " diacetate*, m. p. 231—233°, $[\alpha]_D$ +50° (*c*, 1·73) (Found: C, 63·1; H, 7·85; N, 2·6; Ac, 14·05. $C_{33}H_{49}O_{10}N,\frac{1}{2}CH_3{\cdot}OH$ requires C, 63·3; H, 8·1; N, 2·2; Ac, 13·5%).

Stability of Cevagenin Orthoacetate Diacetate to Chromic Acid.—Cevagenin orthoacetate diacetate (57 mg.) (Stoll and Seebeck, *Helv. Chim. Acta*, 1952, **35**, 1942) in " AnalaR " acetic acid (10 ml.) was treated at room temperature with chromium trioxide equivalent to twice that required for the oxidation of one secondary hydroxyl group. After 6 hr. no significant amount of oxidant had been consumed (titration) and the cevagenin orthoacetate diacetate was recovered unchanged (m. p., mixed m. p., and rotation).

Reduction of Cevine Orthoacetate Triacetate with Lithium and Liquid Ammonia.—Cevine orthoacetate triacetate (110 mg.) in dioxan (5 ml.; distilled over sodium) was added to a solution of lithium (80 mg.) in liquid ammonia (20 ml.), and the solution stirred for 10 min. with exclusion of moisture. The excess of lithium was destroyed by ammonium chloride, the ammonia allowed to evaporate, and the residue extracted with water and chloroform. Crystallisation of the chloroform-soluble material from ether–ethanol gave *dihydrocevine orthoacetate*, m. p. 262—264° (decomp.; sintering at 185°), $[\alpha]_D$ +48° (*c*, 0·64) (Found: C, 64·7; H, 8·55; N, 2·35; Ac, 7·7. $C_{29}H_{45}O_8N$ requires C, 65·0; H, 8·45; N, 2·6; Ac, 8·05%). In a second experiment the time of reduction was prolonged to 30 min. without altering the properties of the product, $[\alpha]_D$ +47° (*c*, 1·90). Dihydrocevine orthoacetate did not reduce Fehling's solution.

Dihydrocevine orthoacetate (60 mg.) was heated on the steam-bath for 2 hr. with pyridine (1 ml.) and acetic anhydride (2 ml.). The excess of reagents was removed *in vacuo* and the product crystallised from ether–light petroleum (b. p. 40—60°), to give *dihydrocevine orthoacetate triacetate*, m. p. 277—279°, $[\alpha]_D$ +81° (*c*, 0·84) (Found: C, 63·9; H, 7·85; N, 1·85; Ac, 25·2. $C_{35}H_{51}O_{11}N$ requires C, 63·5; H, 7·75; N, 2·1; Ac, 25·95%). The triacetate (16 mg.) in " AnalaR " acetic acid (2 ml.) 0·05N with respect to chromium trioxide consumed no significant amount of oxidant during 70 min. at room temperature.

Methanolysis of Cevine Triacetate.—The triacetate (Barton and Brooks, *Chem. and Ind.*, 1953, 1366; Barton, Brooks, and Fawcett, *J.*, 1954, 2137) (1·05 g.) in methanol (100 ml.) was left for 8 hr. at room temperature. Water (20 ml.) was added and the solution left overnight. Most of the methanol was removed *in vacuo* and the resulting aqueous suspension was extracted with chloroform. Crystallisation of the product from aqueous acetone afforded *cevine* 3 : 4-

diacetate (500 mg.), m. p. 275—278° (decomp.: sintering at 160°, and resolidifying at 190—200°), $[\alpha]_D$ +14° (*c*, 1·21 in acetone), +28° (*c*, 1·18 in EtOH) (Found: C, 63·05; H, 7·9; N, 2·35; Ac, 14·75. $C_{31}H_{47}O_{10}N$ requires C, 62·7; H, 8·0; N, 2·35; Ac, 14·5%).

Cevine 3 : 4-diacetate (167 mg.) in carbon tetrachloride (25 ml.) was treated with chromium trioxide solution (10 ml.; 0·16N) in 98·5% aqueous acetic acid for 40 min. at room temperature (the appropriate control experiments were run at the same time). Crystallisation of the product from ethanol gave the required *ketone* as prisms, m. p. 279—280° (decomp.), $[\alpha]_D$ +17° (*c*, 1·18), +20° (*c*, 1·12), −20° (*c*, 0·70 in 1 : 1 acetone–chloroform) (Found: C, 62·8; H, 7·35; N, 2·45. $C_{31}H_{45}O_{10}N$ requires C, 62·9; H, 7·65; N, 2·35%).

In a related alcoholysis experiment cevine triacetate (70 mg.) was dissolved in 96% ethanol (5·0 ml.) ($[\alpha]_D$ of solution +31°), triethylamine (12 mg.; 1·1 mols.) in water (0·2 ml.) added, and the solution left at room temperature. After 14 days the rotation had fallen to +25°, unchanged after a further 6 months. Cevine 3 : 4-diacetate (60%), identified by m. p., mixed m. p., and rotation {$[\alpha]_D$ +14° (*c*, 1·00 in acetone)}, was isolated without difficulty from the product. Similarly cevine triacetate (79 mg.) in 96% ethanol (5·0 ml.) containing 0·59N-sulphuric acid (0·40 ml.; 2 equivs.) had $[\alpha]_D$ +35° unchanged during 6 months at room temperature; unchanged cevine triacetate (64%), identified by m. p., mixed m. p., and rotation, $[\alpha]_D$ +21° (*c*, 1·70 in acetone), was recovered.

Lead Tetra-acetate and Periodic Acid Titrations.—The general procedures were as in Part I. The lead tetra-acetate oxidations were carried out in pure acetic acid at concentrations approx. 0·005M with respect to the substrate and approx. 0·015M with respect to lead tetra-acetate.

The periodic acid oxidations were carried out in 1 : 4 ethanol–water at concentrations approx. 0·02M of pure periodic acid and 0·005M with respect to substrate. The amount of periodic acid consumed depended very much upon the pH of the solution. Two different techniques were therefore employed, (*a*) making no addition of sodium hydrogen carbonate and (*b*) adjusting the pH to 7·0 by sodium hydrogen carbonate. Illustrative results are summarised in Table 3. It was eventually discovered that no consumption of oxidant occurred at all until the sodium hydrogen carbonate was added. The following experiment is illustrative. Cevine triacetate (100 mg.) was dissolved in 1 : 4 ethanol–water (10 ml.) made 0·05N with respect to periodic acid. After 10 min. an aliquot portion (1 ml.) was titrated in the usual way and indicated the consumption of 0·95 mol. of periodic acid. The remainder of the solution (9 ml.) was diluted with water and repeatedly extracted with chloroform. Crystallisation from aqueous methanol gave back cevine triacetate (65 mg.), identified by m. p., mixed m. p., and rotation {$[\alpha]_D$ +21° (*c*, 0·97 in acetone)}. The recovered material was similarly oxidised with (in the aliquot portion) the apparent consumption of 1 mol. of periodic acid, but the starting material was given back on processing without sodium hydrogen carbonate being added. A similar oxidation, adjusted to pH 6·8 with sodium hydrogen carbonate, did not afford starting material; the uptake of periodic acid after 10 min. was 0·95 mol.

Action of Alkali on the Ketone (XII; R = *Angeloyloxy*) *from Cevadine Orthoacetate Acetate and Related Transformations.*—The ketone (XII; R = angeloyloxy) (500 mg.) in methanol (180 ml.) was treated with 5N-sodium hydroxide (20 ml.) at room temperature (20°) for exactly 2 min. The solution was then acidified with acetic acid and concentrated *in vacuo* to 50 ml. The pH was adjusted to 8 and the solution extracted with chloroform. The product crystallised from methanol, to give the unsaturated *ketone* (XIII; R = angeloyloxy) as needles, m. p. 211—212°, $[\alpha]_D$ +39° (*c*, 1·28), $\lambda_{max.}$ 221 mμ (ε 16,800), $\lambda_{max.}$ (compensated for unsaturated-ester absorption by using an equivalent quantity of cevadine in the alcohol blank) 236 mμ (ε 10,200) (Found: C, 67·55; H, 8·05; angeloyl, 12·45. $C_{32}H_{45}O_8N$ requires C, 67·25; H, 7·95; angeloyl, 14·5%). On more prolonged treatment with alkali the unsaturated ketone was transformed into a further compound having $\lambda_{max.}$ 295 mμ, $E^{1\%}_{1\,cm.}$ 500 and giving a positive ferric chloride test. This substance could only be obtained crystalline as a chloroform solvate of indefinite m. p. and $[\alpha]_D$ +172° (*c*, 1·7), +171° (*c*, 1·13). Satisfactory analytical data could not be obtained.

The unsaturated ketone (XIII; R = angeloyloxy) (see above) (59 mg.) in ethyl acetate (5 ml.) was hydrogenated with 10% palladised charcoal; uptake of hydrogen ceased after 0·92 mol. had been absorbed. Crystallisation of the product from chloroform–light petroleum (b. p. 60—80°) gave the *ketone* (XIII; R = α-methyl-*n*-butyroyloxy) as needles m. p. 224—225°, $[\alpha]_D$ +33° (*c*, 0·89), $\lambda_{max.}$ 238 mμ (ε 12,500) (Found: C, 67·05; H, 8·25; N, 2·7. $C_{32}H_{47}O_8N$ requires C, 67·0; H, 8·25; N, 2·45%).

Oxidation of Dihydrocevadine Orthoacetate Acetate.—Cevadine orthoacetate acetate (1·0 g.) in ethyl acetate (50 ml.) was hydrogenated with 10% palladised charcoal for 40 hr. Crystallisation of the product from aqueous acetone gave *dihydrocevadine orthoacetate acetate*, m. p. 278—279°,

$[\alpha]_D$ +63° (*c*, 2·06), no selective absorption in the ultra-violet (Found: C, 65·05; H, 7·95. $C_{36}H_{53}O_{10}N$ requires C, 65·55; H, 8·1%).

Dihydrocevadine orthoacetate acetate (257 mg.) was oxidised in carbon tetrachloride–acetic acid as in the analogous cases described above (uptake 1·88 equiv.). The product, crystallised from ethanol, gave the required *ketone* (XII; R = α-methyl-*n*-butyroyloxy) (186 mg.) as needles, m. p. 252—253° (decomp.), $[\alpha]_D$ +50° (*c*, 1·15), +50° (*c*, 0·98) (Found: C, 65·6; H, 7·5; N, 2·35. $C_{36}H_{51}O_{10}N$ requires C, 65·75; H, 7·8; N, 2·15%). In a second experiment 1·13 g. (82%) of the ketone, $[\alpha]_D$ +49° (*c*, 1·16), was obtained from 1·37 g. of the parent alcohol.

The above-mentioned ketone (200 mg.) was treated with methanol (80 ml.) and sodium hydroxide solution (5N; 10 ml.), as described in the experiment above. The product was identified as the unsaturated ketone (XIII; R = α-methyl-*n*-butyroyloxy) by m. p., mixed m. p., rotation {$[\alpha]_D$ +32° (*c*, 1·19)}, absorption spectrum, and crystal form.

Rearrangement of Dihydrocevine Orthoacetate to Dihydrocevine iso*Orthoacetate and Related Transformations.*—Dihydrocevine orthoacetate (191 mg.) was dissolved in N-sulphuric acid (5 ml.) and left at room temperature (20°) for 30 min. Isolation of the product by adjustment of the pH to 9 and extraction with chloroform followed by crystallisation from methanol–ether–light petroleum (b. p. 40—60°) afforded *dihydrocevine* iso*orthoacetate* (160 mg.), m. p. 265—266°, $[\alpha]_D$ −14° (*c*, 1·04) (Found: C, 65·25; H, 8·45; N, 2·75; Ac, 6·6. $C_{29}H_{45}O_8N$ requires C, 65·0; H, 8·45; N, 2·6; Ac, 8·0%). The same rearrangement was effected by dissolving dihydrocevine orthoacetate in acetic acid at room temperature and leaving it for 1 hr.

Crude cevagenin orthoacetate, $[\alpha]_D$ *ca.* +23° in EtOH, was prepared without difficulty by following the directions of Stoll and Seebeck (*Helv. Chim. Acta*, 1952, **35**, 1942). A portion (40 mg.) was dissolved in N-sulphuric acid (1 ml.). After 1 min. N-ammonia was added. Extraction with chloroform gave a product, $[\alpha]_D$ −18° (*c*, 1·07 in EtOH), which readily afforded cevagenin orthoacetate, m. p. 180—186°, $[\alpha]_D$ −38° (*c*, 1·04 in EtOH), on crystallisation from acetone (needles) or from methanol (prisms). Repetition of the experiment, but leaving the base in N-sulphuric acid for (*a*) 20 and (*b*) 60 min., gave the same result.

In a comparable experiment cevine orthoacetate (205 mg.) was treated with sulphuric acid for 1 min. in the same way. The crude product was heated at 90° with acetic acid (5 ml.) for 1 hr. (to reclose the opened orthoacetate ring; cf. Part II). Working up gave back starting material, identified by m. p., mixed m. p., and rotation.

The effect of N-sulphuric acid (2 ml.) on cevadine orthoacetate acetate (85 mg.) (20 min. at room temperature) was studied in the same way. After reclosure of the orthoacetate grouping cevadine orthoacetate acetate, identified by m. p., mixed m. p., and rotation, was recovered unchanged.

Cevine 16-*Acetate Perchlorate.*—Cevine 3 : 16-diacetate (170 mg.) in ethyl acetate (2·0 ml.) was treated with a solution of aqueous perchloric acid (72%; 0·1 ml.) in ethyl acetate (1·0 ml.). The solution was evaporated *in vacuo* at room temperature and the residue triturated with ether. The resulting solid was crystallised from hot water, to afford *cevine* 16-*acetate perchlorate* (90 mg.) as plates, m. p. 280—282° (decomp.), $[\alpha]_D$ −5°, −6° (*c*, 1·46 and 0·99 respectively in MeOH) (Found: C, 53·05; H, 7·05; Cl, 5·8; Ac, 6·9. $C_{29}H_{45}O_9N,HClO_4$ requires C, 53·4; H, 7·1; Cl, 5·45; Ac, 6·6%). The constitution of this compound is established by the data given above and by the lead tetra-acetate oxidation results summarised in Table 2.

Two of us (C. J. W. B. and P. de M.) are indebted to Messrs. Glaxo Laboratories Limited for the Fellowship support which made this work possible.

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Studies on the Diels–Alder Reaction. Part III. The Stereochemistry of Perhydro-1 : 4-dioxophenanthrene and Related Compounds.*

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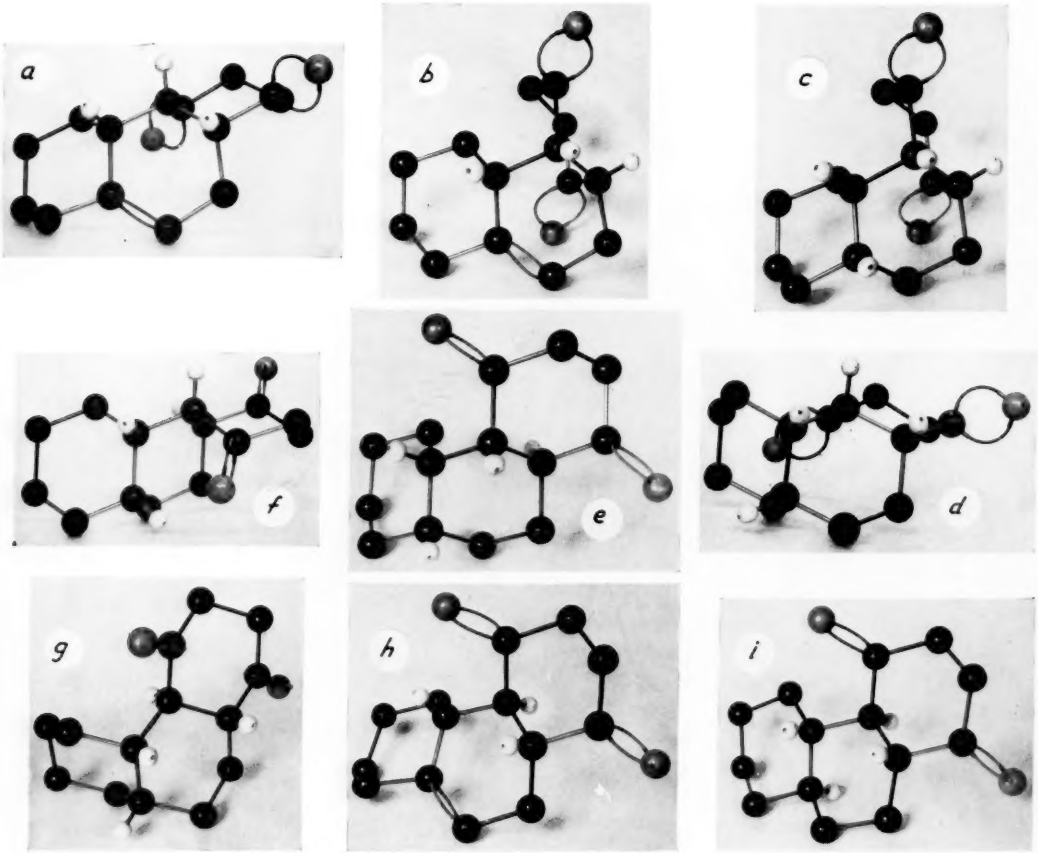
Starting from the stereochemically unstable *cis-syn*-$\Delta^{9(14)}$-dodecahydro-1 : 4-dioxophenanthrene (I), selective methods of reduction and oxidation, together with controlled stereochemical inversions at points of ring-fusion rendered labile by the presence of adjacent carbonyl groups, have given access to a series of five perhydro-1 : 4-dioxophenanthrenes and related hydroxyketones. Interconversions by way of characterised intermediates have made possible a logical assignment of structures to these stereoisomers, based on current views concerning the stereochemistry of the *cyclo*hexane ring and related fused ring systems, and provide experimental evidence for the following stability sequence for the five perhydro-1 : 4-dioxophenanthrenes and related hydroxyketones: *trans-anti-trans* > *trans-syn-cis* > *cis-anti-cis* > *trans-anti-cis* > *cis-syn-cis*.

On the basis of the now well-accepted premises that the *cyclo*hexane ring is significantly more stable in the chair than in the boat form and that substituents on the ring are more stable in the equatorial than in the axial conformation (cf. Hassel, *Research*, 1950, **3**, 504), Johnson (*Experientia*, 1951, **7**, 315) has suggested, assuming all three rings to have the chair conformation, that the relative stabilities of perhydrophenanthrenes should follow the order: *trans-anti-trans* > *trans-syn-cis* = *trans-anti-cis* > *cis-anti-cis* > *cis-syn-cis*. Following Turner's treatment of *trans*- and *cis*-decalin (*J. Amer. Chem. Soc.*, 1952, **74**, 2118), which, in good agreement with experiment, were estimated to differ from each other in energy by 2·4 kcal. owing to three skew interactions, Johnson (*ibid.*, 1953, **75**, 1498) has, further, assigned energy differences to the perhydrophenanthrenes on the basis of 0·8 kcal. per skew interaction (Pitzer, *Chem. Reviews*, 1940, **27**, 39; Becket, Pitzer, and Spitzer, *J. Amer. Chem. Soc.*, 1947, **69**, 2488) as follows: *trans-anti-trans*, 0; *trans-syn-cis* and *trans-anti-cis*, 2·4 kcal.; *cis-anti-cis*, 4·0 kcal.; and *cis-syn-cis*, *ca.* 6·4 kcal. The *trans-syn-trans*-conformation is incapable of existing with the central ring (ring B) in the chair form and the energy difference for this form must exceed 5·6 kcal., the energy difference between the chair and the boat form of *cyclo*hexane (Becket *et al.*, *loc. cit.*). As we had ready access to *cis-syn*-$\Delta^{9(14)}$-dodecahydro-1 : 4-dioxophenanthrene (I) (Part I, *J.*, 1952, 642), we were in a favourable position to demonstrate, by suitable choice of experimental conditions, a stability sequence of the above nature, the configuration of (I) being assigned on the sole basic assumptions (i) that the course of the Diels–Alder reaction between vinyl*cyclo*hexene and benzoquinone followed the Alder rules for diene additions (Alder and Stein, *Angew. Chem.*, 1937, **50**, 510), and (ii) that the mild conditions used for the reduction of the 2 : 3-double bond in the resulting *cis-syn*-$\Delta^{2:9(14)}$-decahydro-1 : 4-dioxophenanthrene (II) with zinc powder and glacial acetic acid had caused no stereochemical change at position(s) 11 and/or 12. Fortunately the reaction between vinyl*cyclo*hexene and benzoquinone was relatively rapid and there can be no doubt that (II) had the *cis-syn*-structure, but stereoisomerisation of the adduct initially formed may occur in slower diene-addition reactions of this type (cf. Lukes, Poos, and Sarett, *J. Amer. Chem. Soc.*, 1952, **74**, 1402); it may be stated now, however, that the above assumptions seem to have been fully justified and that the results to be described below do not appear to be capable of interpretation on any other basis. The 9(14)-position of the double bond in (I) was demonstrated by the presence in its infrared absorption spectrum of a strong band at 816 cm.$^{-1}$.

We have previously described (Part I) the catalytic hydrogenation of *cis-syn*-$\Delta^{2:9(14)}$-decahydro-1 : 4-dioxophenanthrene (II) over palladised strontium carbonate to a perhydro-1 : 4-dioxophenanthrene, m. p. 108—109° [also obtained on hydrogenation of *cis-syn*-$\Delta^{9(14)}$-dodecahydro-1 : 4-dioxophenanthrene (I) under mild conditions], to which the *cis-syn*-

* Part II, *J.*, 1952, 1610.



a, *b*: cis-syn-$\Delta^{9(14)}$-*Dodecahydro*-**1** : **4**-*dioxophenanthrene* (I).
c, *d*: cis-syn-cis-*Perhydro*-**1** : **4**-*dioxophenanthrene* (III).
e: trans-syn-cis-*Perhydro*-**1** : **4**-*dioxophenanthrene* (V).
f: cis-anti-cis-*Perhydro*-**1** : **4**-*dioxophenanthrene* (XII).
g: trans-anti-cis-*Perhydro*-**1** : **4**-*dioxophenanthrene* (XIII).
h: trans-anti-$\Delta^{9(14)}$-*Dodecahydro*-**1** : **4**-*dioxophenanthrene* (XXI).
i: trans-anti-trans-*Perhydro*-**1** : **4**-*dioxophenanthrene* (XXIII).

For the sake of clarity hydrogen atoms are only shown at the points of ring fusion.

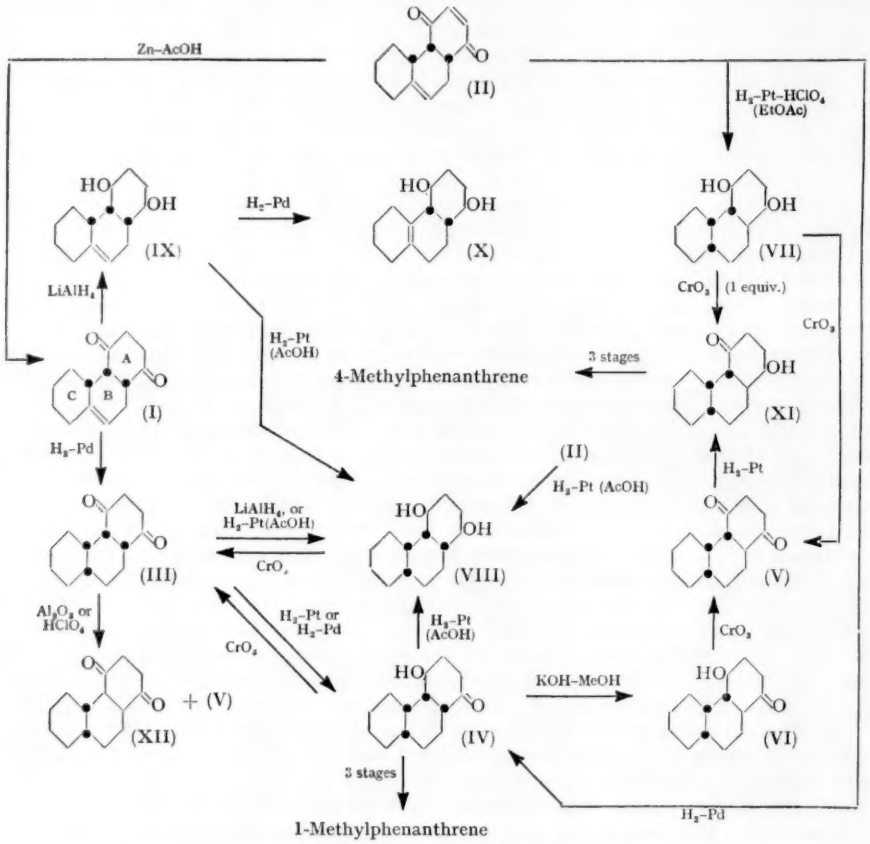
[*To face p.* 3961.

trans-structure was provisionally assigned, with the implication, which we pointed out, that ring A would not have interfered with the hydrogenation of the 9(14)-double bond in (I) by catalyst hindrance (cf. Linstead, Doering, Davis, Levine, and Whetstone, *ibid.*, 1942, **64**, 1985; Linstead and Whetstone, *J.*, 1950, 1428). In (I), carbon atoms $C_{(8)}$, $C_{(9)}$, $C_{(10)}$, $C_{(13)}$, and $C_{(14)}$ are coplanar because of the geometry of the double bond, and there are two possible conformations; in one of these (Fig. *a*) carbon atoms $C_{(1)}$, $C_{(4)}$, and $C_{(5)}$, considered as substituents of ring B, occupy respectively equatorial, axial, and quasi-equatorial positions, while in the other (Fig. *b*) the same substituents are respectively in axial, equatorial, and quasi-axial positions (for the terms " quasi-equatorial " and " quasi-axial," see Barton, Cookson, Klyne, and Shoppee, *Chem. and Ind.*, 1954, 21). The former conformation (Fig. *a*) is therefore the preferred one and it is favoured by experimental evidence to be described below, but both models (Fig. *a* and *b*) show ring A of (I) to be folded backwards roughly at right angles to the general plane of rings B and C in such a way as to cause quite marked catalyst hindrance, and the product of hydrogenation of (I) must therefore be *cis-syn-cis*-perhydro-1 : 4-dioxophenanthrene (diketone A) (III) (Fig. *c* or *d*), derived, theoretically, from the least stable of five (out of the six possible) perhydrophenanthrenes * and having carbonyl groups adjacent to, and rendering stereochemically labile, two points of ring fusion. Catalytic hydrogenation of (III) in acetic acid over Adams's platinum oxide catalyst and reduction with lithium aluminium hydride gave the same *cis-syn-cis*-perhydro-1 : 4-dihydroxyphenanthrene (VIII), m. p. 134—135°, but hydrogenation in neutral solution gave a perhydro-4-hydroxy-1-oxophenanthrene, m. p. 138—139° (Part I), which retained the configuration of (III), since (III) resulted on oxidation with chromic acid, and which must therefore now be assigned the *cis-syn-cis*-structure (IV). The partial reduction of (III) to (IV) shows the 4-carbonyl group of (III) to be the less hindered, thus favouring the first of the two conformations shown (Fig. *c*) rather than the second (Fig. *d*). Treatment of the hydroxy-ketone (IV) with boiling 1% methanolic potassium hydroxide gave a stereoisomeric hydroxy-ketone, m. p. 141—142°, which could have been due either to inversion at $C_{(11)}$, as we had previously suggested, or, as kindly suggested by Professor W. S. Johnson (personal communication), to epimerisation at $C_{(4)}$, the latter being the more probable alternative on the basis of *cis-syn-trans*-structures for the above perhydro-1 : 4-dioxophenanthrene (diketone A) and perhydro-4-hydroxy-1-oxophenanthrene, m. p. 138—139°, although the conditions used in the alkaline stereoisomerisation were relatively mild. The latter alternative was excluded and the former verified, however, by an experiment, of which the significance had also been noted independently by Professor Johnson, namely, the oxidation of the hydroxy-ketone, m. p. 141—142°; this gave a diketone (diketone B), which was distinct from diketone A and must therefore have been the more stable *trans-syn-cis*-perhydro-1 : 4-dioxophenanthrene (V) (Fig. *e*), and the hydroxy-ketone, m. p. 141—142°, was therefore *trans-syn-cis*-perhydro-4-hydroxy-1-oxophenanthrene (VI). Diketone B was identical with the diketone obtained by oxidation with chromium trioxide of the perhydro-1 : 4-dihydroxyphenanthrene, m. p. 212° (VII), obtained by exhaustive hydrogenation of *cis-syn*-$\Delta^{2:9(14)}$-decahydro-1 : 4-dioxophenanthrene (II) over Adams's platinum oxide catalyst in ethyl acetate in the presence of perchloric acid (Part I), and, obviously, inversion at $C_{(11)}$ had occurred during the catalytic hydrogenation of (II) to (VII). This observation throws some light on the variable yields of *cis-syn-cis*-perhydro-1 : 4-dihydroxyphenanthrene (VIII) (isolated as the dibenzoate) obtained when (II) was hydrogenated over Adams's platinum oxide catalyst in acetic acid in presence of a trace of perchloric acid (Part I), and treatment with perchloric acid was subsequently carried out deliberately as a test for stereochemical stability in ketones described in the present communication.

Reduction of *cis-syn*-$\Delta^{9(14)}$-dodecahydro-1 : 4-dioxophenanthrene (I) with lithium

* It may be noted that the six possible perhydrophenanthrenes can give rise theoretically to eight distinct optically inactive 1 : 4-dioxo-derivatives, since *trans-syn-cis-* and *trans-anti-cis*-perhydrophenanthrene can both give rise to two perhydro-1 : 4-dioxophenanthrenes, depending upon whether the *cis-* or the *trans*-fused side-ring bears the two carbonyl groups. No derivative of *trans-syn-trans*-perhydrophenanthrene was encountered in this investigation and no further reference will be made to this structure.

aluminium hydride gave *cis-syn*-$\Delta^{9(14)}$-dodecahydro-1 : 4-dihydroxyphenanthrene (IX), which gave only a monobenzoate and a monotoluene-*p*-sulphonate in contrast with *cis-syn-cis*-perhydro-1 : 4-dihydroxyphenanthrene (VIII) which readily gave a dibenzoate (Part I). Attempted catalytic hydrogenation of (IX) over palladised strontium carbonate resulted



in a negligible uptake of hydrogen and migration of the double bond to an inert position to give a substance, presumably *cis*-Δ^{13}-dodecahydro-1 : 4-dihydroxyphenanthrene (X), showing no infra-red absorption band at ~820 cm.$^{-1}$ characteristic of a trisubstituted ethylene. Double-bond migrations of a similar nature under hydrogenation conditions have been observed amongst unsaturated steroids (cf. Fieser and Fieser, " Natural Products related to Phenanthrene," Reinhold Publ. Corpn., New York, 1949, pp. 240, 249, 624; Rosenkranz, Romo, Batres, and Djerassi, *J. Org. Chem.*, 1951, **16**, 300), and hydrogenation of (IX) in acetic acid in presence of Adams's platinum oxide catalyst gave (X) and *cis-syn-cis*-perhydro-1 : 4-dihydroxyphenanthrene (VIII) as major products, while minor products may have resulted from further shifts of the double bond, as observed in steroids (cf. Fieser and Fieser, *op. cit.*). The formation of (VIII) from (IX) in the latter hydrogenation shows these two compounds to share the same configurations at $C_{(1)}$ and $C_{(4)}$, a point of interest in relation to their behaviour towards oxidation which will be discussed later. On the basis of the preferred conformation (Fig. *a*) for *cis-syn*-$\Delta^{9(14)}$-dodecahydro-1 : 4-dioxophenanthrene (I) one would expect the 4-hydroxyl group of *cis-syn*-$\Delta^{9(14)}$-dodecahydro-1 : 4-dihydroxyphenanthrene (IX), being produced in the reduction of a hindered carbonyl

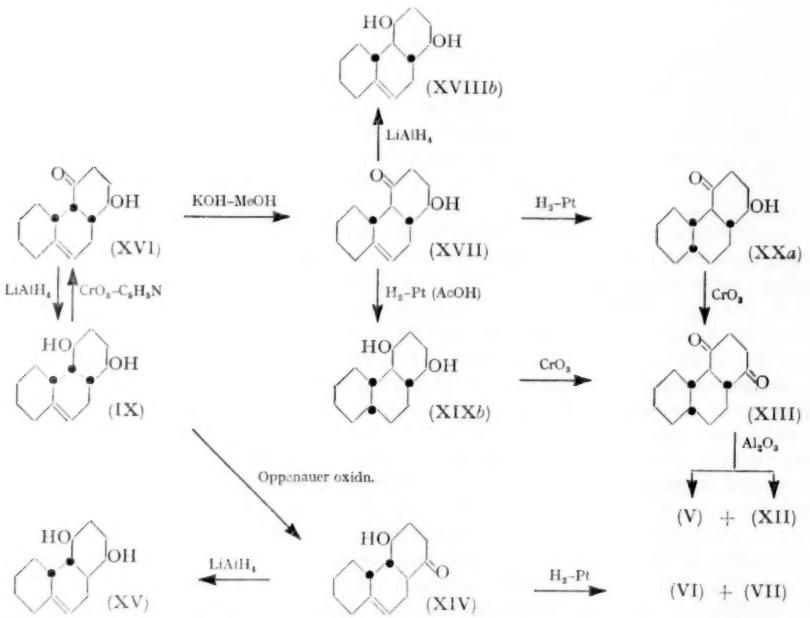
group, to occupy the axial position, and the 1-hydroxyl group to be equatorial, since it arises by reduction of an unhindered carbonyl group. From this line of reasoning it follows that the two hydroxyl groups in (IX) are in *trans*-position to the adjacent bridgehead hydrogen atoms and in *cis*-relation to each other, in agreement with relations experimentally established for the analogous reduction with lithium aluminium hydride of *cis*-6-ethoxy-Δ^6-octahydro-5-methyl-1 : 4-dioxonaphthalene (Beyler and Sarett, *J. Amer. Chem. Soc.*, 1952, **74**, 1406).

Hydrogenation of *trans-syn-cis*-perhydro-1 : 4-dioxophenanthrene (diketone B) (V) under mild conditions over Adams's platinum oxide catalyst gave a hydroxy-ketone, m. p. 173—174°, which, as it could be converted by marking the position of the carbonyl group with methylmagnesium iodide followed by dehydration and dehydrogenation into 4-methylphenanthrene, must have been *trans-syn-cis*-perhydro-1-hydroxy-4-oxophenanthrene (XI), isomeric with (VI), indicating the 1-carbonyl group of diketone B (V) to be the less hindered (cf. Fig. *e*). The partial oxidation with one equivalent of chromic acid of *trans-syn-cis*-perhydro-1 : 4-dihydroxyphenanthrene (VII) to *trans-syn-cis*-perhydro-1-hydroxy-4-oxophenanthrene (XI) is doubtless due to the fact that the 4-hydroxyl group in (VII) has the axial configuration and that the 1-hydroxyl group is equatorial (cf. Barton, *Experientia*, 1950, **6**, 316; *J.*, 1953, 1027). As *trans-syn-cis*-perhydro-1-hydroxy-4-oxophenanthrene (XI) was recovered unchanged on treatment with hot 10% methanolic potassium hydroxide, it appears, in accordance with Johnson's stability sequence, to be more stable than the *cis-anti-cis*-structure, into which it would have passed.

Passage of *cis-syn-cis*-perhydro-1 : 4-dioxophenanthrene (diketone A) (III) in benzene–light petroleum over alkaline alumina, or treatment in ethyl acetate solution with a trace of perchloric acid, gave a mixture of two stereoisomeric diketones. One of these was identified as *trans-syn-cis*-perhydro-1 : 4-dioxophenanthrene (diketone B) (V), which has been discussed above, and it is formed from (III) by inversion at $C_{(11)}$. The other diketone (diketone C) was a new substance and might have been expected to be that formed from (III) by inversion at $C_{(12)}$, *i.e.*, to be *trans-anti-cis*-perhydro-1 : 4-dioxophenanthrene (XIII) (Fig. *g*); this structure, however, was excluded by the unequivocal preparation of a different diketone (diketone D) having the *trans-anti-cis*-configuration, as described below, and diketone C must therefore have been the product resulting from inversion at both $C_{(11)}$ and $C_{(12)}$, namely *cis-anti-cis*-perhydro-1 : 4-dioxophenanthrene (XII) (Fig. *f*). The *cis-anti-cis*-structure is considered by Johnson (*locc. cit.*) to be less stable than either the *trans-syn-cis*- or the *trans-anti-cis*-configuration, and we have already noted the stability to alkali of *trans-syn-cis*-perhydro-1-hydroxy-4-oxophenanthrene (XI). Diketone C, however, was also obtained, as will be described below, by treatment of *trans-anti-cis*-perhydro-1 : 4-dioxophenanthrene (diketone D) (XIII) with alkaline alumina, so that *cis-anti-cis*-perhydro-1 : 4-dioxophenanthrene (diketone C) (XII) should be considered as having somewhat greater stability than is predictable on a quasi-theoretical basis. As far as we are aware, diketone C is the first *cis-anti-cis*-perhydrophenanthrene derivative to be described (cf. Linstead and Whetstone, *loc. cit.*).

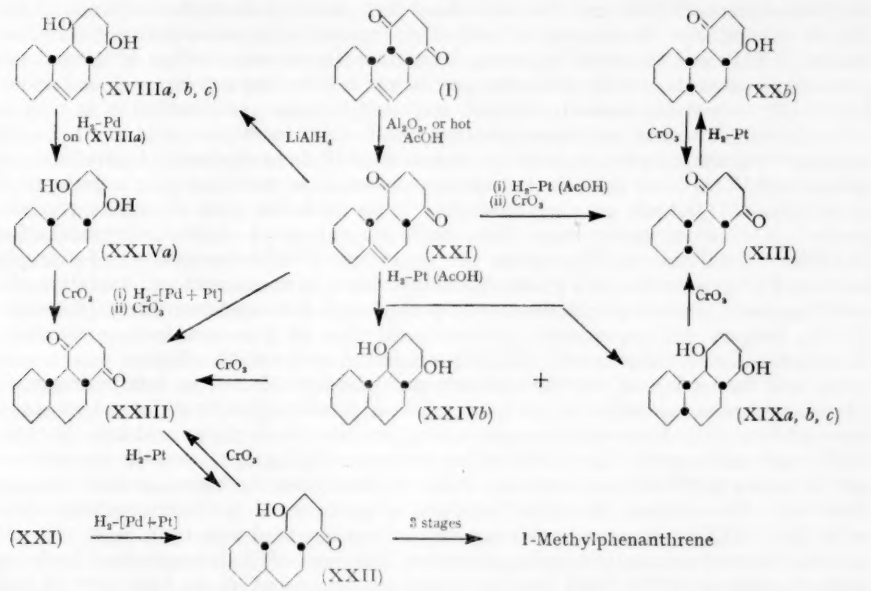
Whereas oxidation of *cis-syn*-$\Delta^{9(14)}$-dodecahydro-1 : 4-dihydroxyphenanthrene (IX) with chromium trioxide in acetic acid gave no recognisable product, the Oppenauer method afforded an unsaturated hydroxy-ketone, m. p. 126—128°, which gave on reduction with lithium aluminium hydride, not (IX), but a stereoisomeric unsaturated diol, m. p. 184—185°, indicating inversion to have taken place adjacent to the carbonyl group introduced during the Oppenauer oxidation in a similar fashion to that observed by Poos, Arth, Beyler, and Sarett (*J. Amer. Chem. Soc.*, 1953, **75**, 422) in an analogous case; furthermore, catalytic hydrogenation of the unsaturated hydroxy-ketone, m. p. 126—128°, over Adams's platinum oxide catalyst to give a mixture of *trans-syn-cis*-perhydro-4-hydroxy-1-oxophenanthrene

(VI) and *trans-syn-cis*-perhydro-1 : 4-dihydroxyphenanthrene (VII) showed it to be *trans-syn*-$\Delta^{9(14)}$-dodecahydro-4-hydroxy-1-oxophenanthrene (XIV), and the new unsaturated diol, m. p. 184—185°, obtained from it by reduction to be *trans-syn*-$\Delta^{9(14)}$-dodecahydro-1 : 4-dihydroxyphenanthrene (XV). As expected, the hydroxy-ketone (XIV), already equilibrated in the Oppenauer oxidation, was stable to methanolic potassium hydroxide. Oxidation of *cis-syn*-$\Delta^{9(14)}$-dodecahydro-1 : 4-dihydroxyphenanthrene (IX) with the chromium trioxide–pyridine reagent (cf. Poos *et al., loc. cit.*) gave a new unsaturated hydroxy-ketone, m. p. 164—167°, shown to have retained the *cis-syn*-configuration by reduction with lithium aluminium hydride to its precursor (IX). It was unstable to alkali, however, and the product of stereoisomerisation was distinct from *trans-syn*-$\Delta^{9(14)}$-do-



decahydro-4-hydroxy-1-oxophenanthrene (XIV); obviously the chromium trioxide–pyridine reagent had effected oxidation at the secondary 4-alcohol group (cf. Poos *et al., loc. cit.*), giving *cis-syn*-$\Delta^{9(14)}$-dodecahydro-1-hydroxy-4-oxophenanthrene (XVI), which had passed on treatment with methanolic potassium hydroxide into the more stable *trans-anti*-$\Delta^{9(14)}$-dodecahydro-1-hydroxy-4-oxophenanthrene (XVII). The above stereospecific oxidations of *cis-syn*-$\Delta^{9(14)}$-dodecahydro-1 : 4-dihydroxyphenanthrene (IX), on the one hand at the secondary 1-alcohol group in the Oppenauer oxidation and, on the other, at the secondary 4-alcohol group with chromium trioxide–pyridine, are in agreement with the suggestion made above, on the basis of the preferred conformation for (I) (Fig. *a*), that the 1-hydroxyl group in (IX) is equatorial, while that at $C_{(4)}$ is axial; moreover, (IX) and (XVI) both gave a monobenzoate and a monotoluene-*p*-sulphonate, and acylation must have taken place at the unhindered 1-hydroxyl group. In contrast, *trans-syn*-$\Delta^{9(14)}$-dodecahydro-4-hydroxy-1-oxophenanthrene (XIV) did not react with toluene-*p*-sulphonyl chloride in pyridine in the usual way since in this substance only the axial 4-hydroxyl group is still present. Reduction of *trans-anti*-$\Delta^{9(14)}$-dodecahydro-1-hydroxy-4-oxophenanthrene (XVII) with lithium aluminium hydride gave a *trans-anti*-$\Delta^{9(14)}$-dodecahydro-1 : 4-dihydroxyphenanthrene, m. p. 194—195° (XVIII*b*), but greater interest attached to the reduction of the 9 : 14-double bond. Catalytic hydrogenation over Adams's platinum oxide catalyst gave a hydroxy-ketone, m. p. 177—177·5°, in neutral solution, and a diol, m. p. 208—210°, in

glacial acetic acid, both of which passed on oxidation with chromic acid into the same new saturated diketone (diketone D). Equilibration of diketone D over alkaline alumina gave a mixture of diketone B and diketone C, together with unchanged diketone D. As diketone B has been shown to be *trans-syn-cis*-perhydro-1 : 4-dioxophenanthrene (V), diketone D must also have a *cis*-fusion of rings B and C, and, as it was derived from *trans-anti*-$\Delta^{9(14)}$-dodecahydro-1-hydroxy-4-oxophenanthrene (XVII), it must have been *trans-anti-cis*-perhydro-1 : 4-dioxophenanthrene (XIII) (Fig. *g*); the diol, m. p. 208—210°, and the hydroxy-ketone, m. p. 177—177·5°, were therefore *trans-anti-cis*-perhydro-1 : 4-dihydroxyphenanthrene (XIX*b*) and *trans-anti-cis*-perhydro-1-hydroxy-4-oxophenanthrene (XX*a*) respectively. Diketones A, B, C, and D all have *cis*-fusion of rings B and C, and since the configurations of diketones A, B, and D are as derived above, diketone C must by exclusion,



as mentioned previously, be the remaining possibility, namely, *cis-anti-cis*-perhydro-1 : 4-dioxophenanthrene (XII), for which the preferred conformation (Fig. *f*) has carbon atoms $C_{(4)}$ and $C_{(5)}$ as axial, rather than equatorial, substituents of ring B (cf. Johnson, *J. Amer. Chem. Soc.*, 1953, **75**, 1498).

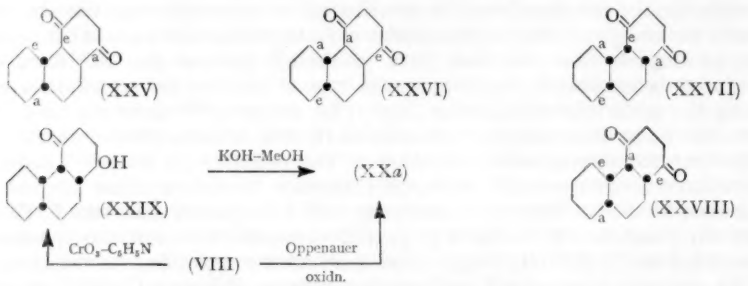
In Part I (*J.*, 1952, 642), a compound designated *trans-anti*-$\Delta^{9(14)}$-dodecahydro-1 : 4-dioxophenanthrene (XXI) was obtained in low yield when *cis-syn*-$\Delta^{2:9(14)}$-decahydro-1 : 4-dioxophenanthrene (II) was reduced with zinc powder in boiling acetic acid solution. The same substance was later obtained from *cis-syn*-$\Delta^{9(14)}$-dodecahydro-1 : 4-dioxophenanthrene (I) in boiling acetic acid, again in low yield, or, in a practicable preparative yield (60—75%), by passing a benzene solution of (I) down a column of alkaline activated alumina under carefully controlled conditions. Subsequent reduction of the substance and the interrelations of the reduction products with each other and with other compounds described in the present communication have confirmed the above structure (XXI) (Fig. *h*). Reduction of (XXI) with lithium aluminium hydride afforded a mixture of diols which could be partially separated by fractional crystallisation and subsequently completely by chromatography on alumina to give three stereoisomeric *trans-anti*-$\Delta^{9(14)}$-dodecahydro-1 : 4-dihydroxyphenanthrenes (XVIII*a*, *b*, *c*,), which can only differ with respect to the configurations at $C_{(1)}$ and $C_{(4)}$. One of these (XVIII*b*) was identical with the diol obtained by reduction of *trans-anti*-$\Delta^{9(14)}$-dodecahydro-1-hydroxy-4-oxophenanthrene (XVII), which

must, from its mode of formation, have the *trans-anti*-structure. Catalytic hydrogenation of *trans-anti*-$\Delta^{9(14)}$-dodecahydro-1 : 4-dioxophenanthrene (XXI) under neutral conditions in presence of a mixture of palladium and platinum catalysts gave a saturated hydroxy-ketone, m. p. 138—140°, and, on chromium trioxide oxidation of the material remaining in the mother-liquors, a new saturated diketone (diketone E), which were interconvertible by hydrogenation and oxidation with chromium trioxide in acetic acid. The hydroxy-ketone, m. p. 138—140°, was shown to be a perhydro-4-hydroxy-1-oxophenanthrene by marking the position of the carbonyl group with methylmagnesium iodide and conversion into 1-methylphenanthrene in the usual way (cf. Part I). As diketone D has been shown to be the *trans-anti-cis*-stereoisomer (XIII), the only remaining structure derivable from a *trans-anti*-$\Delta^{9(14)}$-precursor is the *trans-anti-trans*-one, and the hydroxy-ketone of m. p. 138—140° and diketone E must therefore be *trans-anti-trans*-perhydro-4-hydroxy-1-oxophenanthrene (XXII) and *trans-anti-trans*-perhydro-1 : 4-dioxophenanthrene (XXIII) (Fig. *i*) respectively. In conformity with their expected maximal stability, the hydroxy-ketone (XXII) was recovered unchanged after treatment with boiling 10% methanolic potassium hydroxide or with potassium *tert.*-butoxide in boiling *tert.*-butanol, and diketone E (XXIII) was stable towards alkaline activated alumina, to dissolution in cold concentrated sulphuric acid and reprecipitation, and to dilute perchloric acid in ethyl acetate solution. Catalytic hydrogenation of *trans-anti*-$\Delta^{9(14)}$-dodecahydro-1 : 4-dihydroxyphenanthrene (XVIII*a*) over palladised strontium carbonate in methanol gave a perhydrodiol, m. p. 190—191°, which, as it gave diketone E on oxidation with chromium trioxide in acetic acid, must have been *trans-anti-trans*-perhydro-1 : 4-dihydroxyphenanthrene (XXIV*a*). Catalytic hydrogenation of *trans-anti*-$\Delta^{9(14)}$-dodecahydro-1 : 4-dioxophenanthrene (XXI) over Adams's platinum oxide catalyst in acetic acid and oxidation of the resulting crude product gave *trans-anti-cis*-perhydro- 1: 4-dioxophenanthrene (diketone D) (XIII), but, in one experiment, a small proportion of *trans-anti-trans*-perhydro-1 : 4-dioxophenanthrene (diketone E) (XXIII) was found in the mother-liquors, and a careful study was then made of the intermediate perhydrodiols formed in this hydrogenation. Chromatographic separation on partly deactivated alumina gave four distinct substances; three of these passed on oxidation with chromium trioxide in acetic acid into diketone D (XIII) and therefore had the *trans-anti-cis*-structure (XIX*a*, *b*, *c*), and the remaining one gave diketone E (XXIII) on oxidation and must have been the *trans-anti-trans*-compound (XXIV*b*). The second of these *trans-anti-cis*-perhydro-1 : 4-dihydroxyphenanthrenes, m. p. 211° (XIX*b*), obtained in this experiment was identical with that, m. p. 208—210°, obtained (above) on catalytic hydrogenation of *trans-anti*-$\Delta^{9(14)}$-dodecahydro-1-hydroxy-4-oxophenanthrene (XVII), but the *trans-anti-trans*-compound, m. p. 194—195° (XXIV*b*), was distinct from the *trans-anti-trans*-perhydro-1 : 4-dihydroxyphenanthrene, m. p. 190—191° (XXIV*a*), obtained by catalytic hydrogenation of *trans-anti*-$\Delta^{9(14)}$-dodecahydro-1 : 4-dihydroxyphenanthrene (XVIII*a*).

trans-anti-cis-Perhydro-1 : 4-dioxophenanthrene (diketone D) (XIII) on mild catalytic reduction gave rise to a hydroxy-ketone, m. p. 144—145°, which was stable to 10% alcoholic alkali and reconvertible into diketone D by oxidation with chromium trioxide in acetic acid. This hydroxy-ketone differed from the *trans-anti-cis*-perhydro-1-hydroxy-4-oxophenanthrene (XX*a*) obtained (above) by catalytic hydrogenation of *trans-anti*-$\Delta^{9(14)}$-dodecahydro-1-hydroxy-4-oxophenanthrene (XVII), but inspection of a model of diketone D (Fig. *g*) indicates the greater likelihood of reduction taking place at the 1-carbonyl group than at the 4-carbonyl group; the hydroxy-ketone, m. p. 144—145°, will probably have, as (XX*a*) must have, a keto-group at $C_{(4)}$, and it is therefore considered to be *trans-anti-cis*-perhydro-1-hydroxy-4-oxophenanthrene (XX*b*), the difference between the two compounds (XX*a* and *b*) being associated solely with differing configurations at $C_{(1)}$. In (XX*a*) the 1-hydroxyl group must be axial, being derived by the transformation of a known equatorial hydroxyl group in (XVI) during the conformational change involved in passing from *cis-syn-* (XVI) to *trans-anti*-$\Delta^{9(14)}$-dodecahydro-1-hydroxy-4-oxophenanthrene (XVII) and (XX*a*) (compare Fig. *a* with Fig. *h* and Fig. *g*), whereas in (XX*b*) the 1-hydroxyl group, formed in the hydrogenation under neutral conditions of an unhindered carbonyl group, would be expected to be equatorial.

As we have shown, each of the saturated diketones A (III), B (V), D (XIII), and E (XXIII), on catalytic hydrogenation under mild conditions in neutral solution gives rise exclusively to one hydroxy-ketone, and, for the hydroxy-ketones derived from diketones A, B, and E, the position of the remaining carbonyl group was determined by marking with methylmagnesium iodide, followed by dehydration and dehydrogenation to 1- or 4-methylphenanthrene. In this way *cis-syn-cis*- (diketone A) (III) and *trans-anti-trans*-perhydro-1 : 4-dioxophenanthrene (diketone E) (XXIII) gave 1-methylphenanthrene, indicating greater ease of reduction at the 4-carbonyl group, while *trans-syn-cis*-perhydro-1 : 4-dioxophenanthrene (diketone B) (V) gave 4-methylphenanthrene, indicating greater ease of reduction at the 1-carbonyl group. The relative ease of catalytic reduction of carbonyl groups in these saturated diketones must obviously be primarily dependent on relative accessibility to the catalyst, and, conversely, relative resistance to catalytic reduction must be dependent upon relative degrees of steric hindrance. Barton has discussed the problem of steric hindrance of carbonyl groups in relation to the *trans*-A/B series of steroids, to the 18-*iso*oleanane group of triterpenoids, and to lanostane (*J.*, 1953, 1035), but the problem is not an easy one, particularly with *cis*-fused rings, and mixed *cis*- and *trans*-fused rings. Examination of models (Figure) is helpful when the preferred conformation for the parent saturated hydrocarbon can be readily selected by Johnson's rule (*Experientia*, 1951, **7**, 315), that, considering the peripheral rings as substituents of the central ring, the preferred conformation is the one giving the greater number of equatorial substituents to the central ring, assuming all rings to have the chair form. Although Johnson (*loc. cit.*) discussed only *saturated* fused six-membered ring systems, this type of selection has been illustrated above in choosing the preferred conformation (Fig. *a*) for *cis-syn*-$\Delta^{9(14)}$-dodecahydro-1 : 4-dioxophenanthrene (I), in discussing the reduction of (I) with lithium aluminium hydride, and in interpreting the stereospecific oxidation of the resulting *cis-syn*-$\Delta^{9(14)}$-dodecahydro-1 : 4-dihydroxyphenanthrene (IX) with the chromium trioxide–pyridine reagent and by the Oppenauer method. There is no ambiguity with *trans-syn-cis*- (diketone B) (V) (Fig. *e*), *trans-anti-cis*- (diketone D) (XIII) (Fig. *g*) and *trans-anti-trans*-perhydro-1 : 4-dioxophenanthrene (diketone E) (XXIII) (Fig. *i*), but there are two possible conformations (XXV; XXVI) for *cis-anti-cis*-perhydro-1 : 4-dioxophenanthrene (diketone C) (XII) of which the latter (Fig. *f*) is favoured by energy considerations (cf. Johnson, *J. Amer. Chem. Soc.*, 1953, **75**, 1498). Alternatively, in diketones B, D, and E, one may consider rings A and B of the perhydrophenanthrene ring system as a *trans*-decalin system and apply the same treatment as one would apply to a *cyclo*hexane ring, since the *trans*-decalin ring system with both rings in the chair form has a clearly discernible equatorial plane and axial substituents are as clearly seen as they are in *cyclo*hexane itself (cf. Hassel, *Quart. Reviews*, 1953, **7**, 229). When diketone B (V) (Fig. *e*) is considered in this way, $C_{(5)}$ of the phenanthrene ring system is an axial substituent of rings A and B, considered as a *trans*-decalin, while $C_{(8)}$ of the phenanthrene ring system is an equatorial substituent; the reverse obtains with diketone D (XIII) (Fig. *g*), $C_{(5)}$ being the equatorial and $C_{(8)}$ the axial substituent. In diketone B the axial substituent is attached to the β-carbon atom relative to the 4-carbonyl group, which is therefore hindered as shown experimentally. In diketone D the axial substituent in the γ-position is relatively remote, but the model suggests that it could conceivably hinder as close an approach of the 4-carbonyl as that of the 1-carbonyl group to a catalyst. In the case of diketone E (XXIII) (Fig. *i*) the *trans-anti-trans*-conformation has, like *cyclo*hexane and *trans*-decalin, a clearly discernible general equatorial plane and, as there are no axial substituents apart from hydrogen atoms, no differentiation between the two carbonyl groups of diketone E is feasible on conformational grounds. The fact that preferential reduction takes place at the 4-carbonyl group on catalytic hydrogenation, as noted above, is doubtless, in this case, attributable to van der Waals forces favouring a closer approach of the 4-carbonyl group to the catalyst surface. *cis-syn-cis*-Perhydro-1 : 4-dioxophenanthrene (diketone A) (III), however, presents an interesting case, since there are two equally favoured conformations (derived theoretically from enantiomorphous parent hydrocarbons); in one of these (XXVII) (Fig. *c*), $C_{(4)}$ and $C_{(8)}$ are equatorial substituents of ring B, and in the other (XXVIII) (Fig. *d*) $C_{(1)}$ and $C_{(5)}$ are equatorial. As partial catalytic reduction of (III) gave *cis-syn-cis*-perhydro-4-hydroxy-1-oxophenanthrene the former

conformation (Fig. *c*) would appear to be favoured in (III), involving an eversion of the conformation of the molecule during the hydrogenation of the 9 : 14-double bond in passing from *cis-syn*-$\Delta^{9(14)}$-dodecahydro-1 : 4-dioxophenanthrene (I) (Fig. *a*) to (III) (Fig. *c*). It must be assumed that the saturation of the 9 : 14-double bond, with consequent removal of its coplanarity constraints, confers mobility [in the sense (XXVII) $\rightleftharpoons$ (XXVIII)] on the molecule as a whole, and the preferred conformation (XXVII) (Fig. *c*) of *cis-syn-cis*-perhydro-1 : 4-dioxophenanthrene (III) is based purely on selection of the conformation which appears to offer the lesser hindrance to the 4-carbonyl group. Turning, however, to the corresponding diol, *cis-syn-cis*-perhydro-1 : 4-dihydroxyphenanthrene (VIII), in which the configurations at $C_{(1)}$ and $C_{(4)}$ and the relations of the two hydroxyl groups to the adjacent bridgehead hydrogen atoms are the same as they are in *cis-syn*-$\Delta^{9(14)}$-dodecahydro-1 : 4-dihydroxyphenanthrene (IX), since (IX) could be catalytically hydrogenated to give (VIII), a striking difference is at once apparent, as (VIII) readily formed a dibenzoate, whereas (IX) formed only a monobenzoate and monotoluene-*p*-sulphonate. If our argument concerning the stereochemistry of (IX) is correct, and it appeared to be justified by the stereospecific oxidations of (IX) with the chromium trioxide–pyridine reagent and by the Oppenauer method, then one or other of the hydroxyl groups in (VIII) should be axial if



(VIII) has a unique conformation but as both are readily benzoylated there would appear to be no preference for the conformation adopted by (VIII). Similarly, in contrast with the stereospecific oxidations of (IX), oxidation of (VIII) with the chromium trioxide-pyridine reagent and by the Oppenauer method proceeded non-stereospecifically. In both experiments the product consisted of hydroxy-ketonic and diketonic material. A hydroxy-ketone isolated directly from the chromium trioxide–pyridine oxidation product was *cis-syn-cis*-perhydro-1-hydroxy-4-oxophenanthrene (XXIX), since it gave on stereoisomerisation with alcoholic alkali the previously isolated *trans-anti-cis*-perhydro-1-hydroxy-4-oxophenanthrene (XX*a*). Purification of the remainder of the product by chromatography on alumina afforded diketone B and diketone C, resulting from stereoisomerisation of primarily formed diketone A, while the hydroxy-ketone fraction yielded a further quantity of (XX*a*) and material giving strong presumptive evidence from its infra-red absorption spectrum for the presence of *trans-syn-cis*-perhydro-4-hydroxy-1-oxophenanthrene (VI), arising by stereoisomerisation of *cis-syn-cis*-perhydro-4-hydroxy-1-oxophenanthrene (IV). The product from the Oppenauer oxidation, purified by chromatography on alumina, again gave diketone B (V), diketone C (XII), and the hydroxy-ketone (XX*a*). The high proportion of (XX*a*) in the hydroxy-ketone fraction indicated that little of an isomeric perhydro-4-hydroxy-1-oxophenanthrene could have been present, but the formation of diketones indicated clearly the occurrence of the oxidation of both secondary alcohol groups.

The results obtained in the present work have clearly shown that the five stereoisomeric perhydro-1 : 4-dioxophenanthrenes and related hydroxy-ketones, which we have studied, fall into a stability sequence in which the *cis-syn-cis*- (III) and the *trans-anti-trans*- (XXIII) members are respectively the least and the most stable, with the *cis-anti-cis*- (XII), *trans-anti-cis*- (XIII), and *trans-syn-cis*- (V) members occupying intermediate positions. The formation of *trans-syn-cis*- (V) and *cis-anti-cis*- (XII) in the stereoisomerisation of *cis-syn-cis*-perhydro-1 : 4-dioxophenanthrene (III) involved a single and a double inversion

respectively, but no trace was found of the product (XIII) which should have resulted from the possible alternative single inversion. Likewise, the stereoisomerisation of *trans-anti-cis*-perhydro-1 : 4-dioxophenanthrene (XIII) gave (XII) and (V), again by single and double inversion respectively, but, in this instance, unchanged material (XIII) was also isolated. In both cases (III) and (XIII), however, the product resulting from the double inversion was obtained in the smaller proportion. Obviously the energy differences between *trans-syn-cis-* (V), *cis-anti-cis-* (XII), and *trans-anti-cis*-perhydro-1 : 4-dioxophenanthrene (XIII) are small, but the resistance shown by *trans-syn-cis*-perhydro-1-hydroxy-4-oxophenanthrene (XI) towards alkaline stereoisomerisation points to the *trans-syn-cis-* being more stable than the *cis-anti-cis*-structure; it also points to the fact that *trans-syn-cis-* (V) is unlikely to be an intermediate in the formation of *cis-anti-cis-* (XII) during the stereoisomerisation of *cis-syn-cis*-perhydro-1 : 4-dioxophenanthrene (III). In the following Table there are assembled the significant observations concerning the stability of the various stereoisomeric forms that have emerged from this work, together with the inferences to be drawn from them. One may conclude from these that the stability sequence for the five stereoisomeric perhydro-1 : 4-dioxophenanthrenes and related hydroxy-ketones, which we have studied is : *trans-anti-trans* > *trans-syn-cis* > *cis-anti-cis* > *trans-anti-cis* > *cis-syn-cis*. This sequence differs from Johnson's postulated sequence for the perhydrophenanthrenes in placing the *cis-anti-cis-* before the *trans-anti-cis*-member, and our reason for placing the two diketones in that order is based on the extent to which *trans-anti-cis-* (XIII) appeared to undergo conversion on alkaline alumina into a mixture of *trans-syn-cis-* (V) and *cis-anti-cis-*

Observation	Inference concerning stability
Complete conversion of (III) into (V) + (XII) ...	*trans-syn-cis, cis-anti-cis* > *cis-syn-cis*
Substantial conversion of (XIII) into (V) + (XII)	*trans-syn-cis, cis-anti-cis* > *trans-anti-cis*
Stability of (XXIII)	*trans-anti-trans* > *cis-anti-trans, cis-syn-trans,* (*trans-syn-trans*)
Conversion of (IV) into (VI)	*trans-syn-cis* > *cis-syn-cis*
Conversion of (XXIX) into (XX*a*)	*trans-anti-cis* > *cis-syn-cis*
Stability of (XI)	*trans-syn-cis* > *cis-anti-cis*
Stability of (XXII)	*trans-anti-trans* > *cis-anti-trans*
[Stability of (XX*b*)	*trans-anti-cis* > *cis-syn-cis*]

perhydro-1 : 4-dioxophenanthrene (XII). While Johnson's treatment may apply without reservations to the parent perhydrophenanthrenes, the introduction of carbonyl groups, as in the present series of compounds, may result in some stabilisation of boat forms (cf. Hassel, *Quart. Reviews*, 1953, **7**, 230), as is suggested by the dipole moment of *cyclo*hexane-1 : 4-dione (Le Fèvre and Le Fèvre, *J.*, 1935, 1696), which is unlikely to be due to enolisation (cf., however, Svirbely and Lander, *J. Amer. Chem Soc.*, 1950, **72**, 3756), and by comparison of the dipole moments of androstane- and *ætio*cholane-3 : 17-dione with the calculated values (Nace and Turner, *ibid.*, 1953, **75**, 4063). We are not, however, in a position to decide whether such considerations may, or may not, have a bearing on the relative stabilities of (XII) and (XIII).

Experimental

M. p.s given in the form " m. p. (micro) " were observed on a microscope hot stage, otherwise they were taken in capillary tubes in the usual way. In no case encountered in the present work did the m. p. of a mixture of non-identical substances, individually of similar m. p., fail to show a marked depression.

*Stability of Perhydro-*1 : 4*-dioxophenanthrenes and of Perhydro-*1(*or* 4)*-hydroxy-*4(*or* 1)*-oxophenanthrenes to Stereoisomeric Change.*—In order to demonstrate the stability, or otherwise, of various members of these series, at least one of the following tests was applied : (i) refluxing with 2% (or up to 10%) methanolic potassium hydroxide; (ii) passage down a column of alkaline alumina in a solvent of suitable eluting power; (iii) treatment at room temperature with a dilute solution of perchloric acid in ethyl acetate. The first of these tests was not applicable to the diketones, since, in every case, these substances rapidly gave brown decomposition products under alkaline conditions, possibly through enolisation and dehydrogenation. In the case of the *trans-anti-trans*-compounds more vigorous conditions were applied, as described later.

cis-syn-cis-*Perhydro-*1 : 4*-dihydroxyphenanthrene* (VIII).—A solution of *cis-syn-cis*-perhydro-

1 : 4-dioxophenanthrene (diketone A) (III) (500 mg.) in dry ether (50 c.c.) was added to a stirred solution of lithium aluminium hydride (1 g.) in dry ether (100 c.c.). The mixture refluxed spontaneously for a few seconds and it was then stirred at room temperature for 30 min. After cautious addition of 2N-sulphuric acid (50 c.c.) the ether layer was washed with water, dried, and evaporated, yielding a gum, which readily solidified when seeded with perhydro-1 : 4-dihydroxyphenanthrene, m. p. 134—135° (Part I). One recrystallisation from ethyl acetate–light petroleum gave colourless prisms (440 mg.), m. p. 132—133°, not depressed on admixture with the diol, m. p. 134—135°, obtained previously.

Catalytic reduction of *cis-syn-cis*-perhydro-1 : 4-dioxophenanthrene (diketone A) in acetic acid, with Adams's platinum oxide as catalyst, gave the same *cis-syn-cis*-perhydro-1 : 4-dihydroxyphenanthrene in good yield, as did also *cis-syn-cis*-perhydro-4-hydroxy-1-oxophenanthrene (IV).

Oxidation of cis-syn-cis-*Perhydro-4-hydroxy-1-oxophenanthrene* (IV) *to* cis-syn-cis-*Perhydro-1 : 4-dioxophenanthrene* (*Diketone* A) (III).—The hydroxy-ketone (IV) (Part I) (50 mg.) in acetic acid (5 c.c.) was treated with chromium trioxide (17 mg.) dissolved in a few drops of water. After being kept overnight at room temperature, the product was isolated in ether, and crystallisation from light petroleum gave clusters of needles, m. p. 109—110°, not depressed on admixture with *cis-syn-cis*-perhydro-1 : 4-dioxophenanthrene (diketone A) (III).

Oxidation of trans-syn-cis-*Perhydro-4-hydroxy-1-oxophenanthrene* (VI). trans-syn-cis-*Perhydro-1 : 4-dioxophenanthrene* (V).—The hydroxy-ketone (VI) (90 mg.), obtained by treatment of *cis-syn-cis*-perhydro-4-hydroxy-1-oxophenanthrene (IV) with 1% methanolic potassium hydroxide (Part I), was treated in glacial acetic acid (10 c.c.) with chromium trioxide (60 mg., 2 equivs.) dissolved in a few drops of water. After being kept overnight at room temperature, excess of chromium trioxide was destroyed by addition of a few drops of methanol, the mixture was diluted with water, and the product was recovered in benzene. Crystallisation from light petroleum gave *trans-syn-cis*-perhydro-1 : 4-dioxophenanthrene (V) (40 mg.), m. p. 115—116° (after drying in a vacuum at 80°), not depressed on admixture with the diketone (diketone B) obtained by oxidation of the perhydro-1 : 4-dihydroxyphenanthrene, m. p. 212° (Part I).

Reduction of cis-syn-$\Delta^{9(14)}$-*Dodecahydro-1 : 4-dioxophenanthrene* (I) *with Lithium Aluminium Hydride.* cis-syn-$\Delta^{9(14)}$-*Dodecahydro-1 : 4-dihydroxyphenanthrene* (IX).—*cis-syn*-$\Delta^{9(14)}$-Dodecahydro-1 : 4-dioxophenanthrene (5 g.) in dry ether (100 c.c.) was added to lithium aluminium hydride (5 g.) in dry ether (200 c.c.). After being heated under reflux for an hour, the reaction mixture was cooled, excess of lithium aluminium hydride was destroyed by dilute sulphuric acid, and the ethereal layer was separated, washed with water, dried, and evaporated. The resulting solid residue, on crystallisation from ethyl acetate–light petroleum, gave stout needles (3·7 g.) of cis-syn-$\Delta^{9(14)}$-*dodecahydro-1 : 4-dihydroxyphenanthrene* (IX), m. p. 127—128° (Found : C, 75·9; H, 10·0. $C_{14}H_{22}O_2$ requires C, 75·6; H, 10·0%), showing a strong band at 822 cm.$^{-1}$ and a weak band at 1650 cm.$^{-1}$ in its infra-red absorption spectrum.

The substance (0·85 g.) was treated in dry pyridine (10 c.c.) with toluene-*p*-sulphonyl chloride (1·6 g., 2·2 mols.). After the mixture had been kept at room temperature overnight the product was isolated with the aid of benzene to give an almost quantitative yield of the 1-*monotoluene-p-sulphonic* ester, m. p. 123—126°. Cautious recrystallisation from benzene–light petroleum with the minimum application of heat gave the pure ester in the form of prisms, m. p. 126—127° (Found : C, 67·2; H, 7·5. $C_{21}H_{28}O_4S$ requires C, 67·0; H, 7·5%). Similarly, benzoylation with excess of benzoyl chloride in pyridine gave the 1-*monobenzoate*, which crystallised from benzene–methanol in prisms, m. p. 133—134° (Found : C, 77·1; H, 8·3. $C_{21}H_{26}O_3$ requires C, 77·3; H, 8·0%).

Attempted Catalytic Hydrogenation of cis-syn-$\Delta^{9(14)}$-*Dodecahydro-1 : 4-dihydroxyphenanthrene* (IX). cis-Δ^{13}-*Dodecahydro-1 : 4-dihydroxyphenanthrene* (X).—(a) *With palladised strontium carbonate.* A solution of *cis-syn*-$\Delta^{9(14)}$-dodecahydro-1 : 4-dihydroxyphenanthrene (200 mg.) in methanol (20 c.c.) was shaken in an atmosphere of hydrogen at room temperature and pressure in the presence of freshly reduced palladium–strontium carbonate (500 mg.). Absorption of hydrogen was negligible during 3 hr. On removal of the catalyst and evaporation of the solvent a solid residue was obtained. Extraction with boiling light petroleum left a small gummy residue which was not further investigated. The light petroleum solution, on cooling, deposited clusters of feathery needles (140 mg.), m. p. 105—106°, of an isomeric unsaturated diol; the substance gave a weak colour with tetranitromethane and, as it showed no absorption band in its infra-red absorption spectrum at *ca.* 820 cm.$^{-1}$ (characteristic of a trisubstituted ethylene), it was presumably cis-Δ^{13}-*dodecahydro-1 : 4-dihydroxyphenanthrene* (X) (Found : C, 75·4; H, 10·0. $C_{14}H_{22}O_2$ requires C, 75·6; H, 10·0%).

(b) *With Adams's platinum oxide catalyst.* A solution of *cis-syn*-$\Delta^{9(14)}$-dodecahydro-1 : 4-dihydroxyphenanthrene (2 g.) in glacial acetic acid (50 c.c.) was shaken in hydrogen at room temperature and pressure with Adams's catalyst (100 mg.). Absorption of hydrogen ceased after about 0·5 mol. had been taken up in 2 hr. A gum was obtained on removal of the catalyst and evaporation of the solvent. Chromatography on alumina (Savory & Moore Ltd.; partly deactivated by addition of 6% of water) in benzene gave, as the two major products, *cis-syn-cis*-perhydro-1 : 4-dihydroxyphenanthrene (VIII) (0·4 g.), m. p. 132—134°, and the above *cis*-Δ^{13}-dodecahydro-1 : 4-dihydroxyphenanthrene (X) (0·65 g.), m. p. 105—106°. Two minor components, one crystallising from ethyl acetate–light petroleum in feathery needles, m. p. 210—211°, and one separating from the same solvent in nodules, m. p. 110—113°, were obtained, but in insufficient quantity for full characterisation; they were not, however, identical with any of the other saturated or unsaturated diols described in this paper.

trans-syn-cis-*Perhydro*-1-*hydroxy*-4-*oxophenanthrene* (XI).—(a) *Hydrogenation of* trans-syn-cis-*perhydro*-1 : 4-*dioxophenanthrene* (diketone B) (V). Diketone B (200 mg.) was shaken in methanol (40 c.c.) in an atmosphere of hydrogen at room temperature and pressure with Adams's platinum oxide (50 mg.) until absorption of hydrogen ceased. Removal of the catalyst and solvent gave trans-syn-cis-*perhydro*-1-*hydroxy*-4-*oxophenanthrene* (XI), which separated from ethyl acetate–light petroleum in colourless needles, m. p. 173—174° (Found: C, 75·6; H, 10·0. $C_{14}H_{22}O_2$ requires C, 75·6; H, 10·0%).

(b) *Partial oxidation of* trans-syn-cis-*perhydro*-1 : 4-*dihydroxyphenanthrene* (VII). *trans-syn-cis*-Perhydro-1 : 4-dihydroxyphenanthrene (200 mg.) in glacial acetic acid (30 c.c.) was oxidised overnight at room temperature with chromium trioxide (65 mg., 1·1 equiv.) dissolved in a few drops of water. The product, twice crystallised from benzene–light petroleum, gave *trans-syn-cis*-perhydro-1-hydroxy-4-oxophenanthrene (XI), m. p. 169—171°, not depressed on admixture with that obtained above.

The substance (XI) was recovered unchanged after 2 hours' refluxing with 10% methanolic potassium hydroxide.

Conversion of trans-syn-cis-*Perhydro*-1-*hydroxy*-4-*oxophenanthrene* (XI) *to* 4-*Methylphenanthrene.—trans-syn-cis*-Perhydro-1-hydroxy-4-oxophenanthrene (1·15 g.) was treated in boiling benzene with methylmagnesium iodide (from 1·5 g. of magnesium) by the procedure outlined previously (Part I) for *cis-syn-cis*-perhydro-4-hydroxy-1-oxophenanthrene (IV), except that purification of the product by means of Girard's reagent was not found necessary. The resulting trans-syn-cis-*perhydro*-1 : 4-*dihydroxy*-4-*methylphenanthrene* separated from ethyl acetate in fine colourless needles (0·82 g.), m. p. 205—206° (Found: C, 75·7; H, 11·0. $C_{15}H_{26}O_2$ requires C, 75·6; H, 11·0%). Dehydration by heating with potassium hydrogen sulphate and dehydrogenation with palladium–charcoal in boiling diphenylamine (cf. Part I) gave 4-methylphenanthrene (0·39 g.), which crystallised from methanol in plates, m. p. 51—52° (Found: C, 93·9; H, 6·6. Calc. for $C_{15}H_{12}$: C, 93·7; H, 6·3%). It formed a picrate, m. p. 142—143°, and a styphnate, m. p. 135—136°; Haworth (*J.*, 1932, 1125) records hydrocarbon, m. p. 49—50°, picrate, m. p. 140—141°, and styphnate, m. p. 135°.

Stereoisomerisation of cis-syn-cis-*Perhydro*-1 : 4-*dioxophenanthrene* (*Diketone A*) (III). trans-syn-cis- (*Diketone B*) (V) *and* cis-anti-cis-*Perhydro*-1 : 4-*dioxophenanthrene* (*Diketone C*) (XII).—(a) *With perchloric acid.* A solution of diketone A (200 mg.) in ethyl acetate (20 c.c.) was treated with perchloric acid (0·02 c.c. of 70%) and set aside at room temperature for 6 hr. After dilution with ether and washing with aqueous sodium hydrogen carbonate, the organic layer yielded, on evaporation, a gum which readily solidified on seeding with diketone B. Crystallisation from light petroleum gave woolly needles, m. p. 103—107°, and a further crystallisation from the same solvent gave a mixture of rosettes of fine needles and clusters of stout needles. After hand-sorting, the rosettes of fine needles gave, on crystallisation from light petroleum, *trans-syn-cis*-perhydro-1 : 4-dioxophenanthrene (diketone B) (V), m. p. 114—115°, not depressed on admixture with an authentic specimen, while the clusters of stout needles gave on recrystallisation a new stereoisomer, which, by exclusion, must have been cis-anti-cis-*perhydro*-1 : 4-*dioxophenanthrene* (diketone C) (XII), in the form of colourless plates, m. p. 139—141° (Found: C, 76·1; H, 9·4. $C_{14}H_{20}O_2$ requires C, 76·2; H, 9·1%).

(b) *With alkaline alumina.* Diketone A (0·5 g.) in benzene–light petroleum (1 : 4) was adsorbed on to a column of alkaline alumina (50 g.; Peter Spence & Sons, Ltd., type H). Fractional elution with benzene–light petroleum (1 : 1) gave fractions, all melting between 90° and 109°, recovery of material being virtually quantitative. A product of the same melting range was obtained on allowing a benzene solution of diketone A (0·2 g.) to percolate down a similar column of alumina and eluting it with benzene. The bulked fractions were crystallised from

light petroleum giving, as in (a), a mixture of rosettes of fine needles and clusters of long flattened needles. This mixture was separated by repeated hand-sorting and fractional crystallisation into diketone B, which crystallised in long needles or as rosettes of needles, m. p. 114—115°, not depressed on admixture with specimens obtained by alternative routes, and diketone C, identical with the material isolated in (a) and crystallising in flattened needles, or plates, m. p. 139—140°.

Oppenauer Oxidation of cis-syn-$\Delta^{9(14)}$-*Dodecahydro*-1 : 4-*dihydroxyphenanthrene* (IX). trans-syn-$\Delta^{9(14)}$-*Dodecahydro*-4-*hydroxy*-1-*oxophenanthrene* (XIV).—A solution of *cis*-*syn*-$\Delta^{9(14)}$-dodecahydro-1 : 4-dihydroxyphenanthrene (3·35 g.) in benzene (150 c.c.) was refluxed for 8 hr. with *cyclo*hexanone (35 c.c.) and aluminium *iso*propoxide (3·5 g.). After cooling, water (7 c.c.) was added and the mixture was filtered. The filtrate was washed once with water and evaporated, finally at 130°/0·1 mm. The residue was triturated with benzene–light petroleum, and the resulting solid was collected. Recrystallisation from benzene–light petroleum gave trans-syn-$\Delta^{9(14)}$-*dodecahydro*-4-*hydroxy*-1-*oxophenanthrene* (XIV) (1·12 g.), m. p. 126—128°, depressed on admixture with the starting material (m. p. 127—128°) (Found : C, 76·4; H, 9·0. $C_{14}H_{20}O_2$ requires C, 76·2; H, 9·1%). Chromatography of the mother-liquors on alumina gave a further quantity of the same substance (XIV) (0·3 g.) and unchanged starting material (0·54 g.). The compound (XIV) was recovered unchanged after refluxing for an hour with 10% methanolic potassium hydroxide, and it failed to give a toluene-*p*-sulphonate under the usual conditions.

Reduction of (XIV) (300 mg.) in boiling ethereal solution with lithium aluminium hydride (500 mg.) for an hour, followed by decomposition of the mixture with excess of dilute sulphuric acid and isolation of the ether-soluble product, gave an unsaturated diol (200 mg.), crystallising from ethyl acetate in fine matted needles, m. p. 184—185°, and stereoisomeric with *cis-syn*-$\Delta^{9(14)}$-dodecahydro-1 : 4-dihydroxyphenanthrene (IX); the following experiment showed it to be trans-syn-$\Delta^{9(14)}$-*dodecahydro*-1 : 4-*dihydroxyphenanthrene* (XV) (Found : C, 75·6; H, 10·0. $C_{14}H_{22}O_2$ requires C, 75·6; H, 10·0%).

Catalytic hydrogenation of the unsaturated hydroxy-ketone (XIV) (500 mg.) in methanol (50 c.c.) at room temperature and pressure in presence of Adams's platinum oxide (100 mg.) ceased after the absorption of approximately 1·2 mols. of hydrogen. Removal of the catalyst and solvent gave a solid residue. Crystallisation from benzene–light petroleum gave in poor yield rosettes of feathery needles, which, after two recrystallisations from ethyl acetate, had m. p. 208—210°, not depressed on admixture with *trans-syn-cis*-perhydro-1 : 4-dihydroxyphenanthrene (VII). The mother-liquors on evaporation gave *trans-syn-cis*-perhydro-4-hydroxy-1-oxophenanthrene (VI) (350 mg.), m. p. 141—142°, not depressed on admixture with a specimen obtained by an alternative route (Part I).

Oxidation of cis-syn-$\Delta^{9(14)}$-*Dodecahydro*-1 : 4-*dihydroxyphenanthrene* (IX) *with the Chromium Trioxide–Pyridine Reagent.* cis-syn- (XVI) *and* trans-anti-$\Delta^{9(14)}$-*Dodecahydro*-1-*hydroxy*-4-*oxophenanthrene* (XVII).—*cis-syn*-$\Delta^{9(14)}$-Dodecahydro-1 : 4-dihydroxyphenanthrene (1 g.) in pyridine (10 c.c.) was oxidised with the chromium trioxide–pyridine reagent (from 1·5 g. of chromium trioxide, 4·5 equivs., prepared according to Poos *et al.*, *loc. cit.*) in pyridine (20 c c.) at room temperature overnight. After addition of water and benzene, a flocculent brown precipitate was filtered off and washed well with benzene. The combined benzene solutions were washed free from pyridine with dilute mineral acid, then with water, and evaporated. Crystallisation of the residue from ethyl acetate afforded fine needles (0·54 g.) of cis-syn-$\Delta^{9(14)}$-*dodecahydro*-1-*hydroxy*-4-*oxophenanthrene* (XVI), m. p. 164—167° (Found : C, 76·2; H, 9·3. $C_{14}H_{20}O_2$ requires C, 76·2; H, 9·1%), showing a medium-intensity band at 820 cm.$^{-1}$ in its infrared absorption spectrum. The *benzoate*, obtained by the action of excess of benzoyl chloride in pyridine, separated from ethyl acetate–light petroleum in fine needles, m. p. 175—176° (Found : C, 77·7; H, 7·6. $C_{21}H_{24}O_3$ requires C, 77·8; H, 7·5%), and the *toluene*-p-*sulphonate* crystallised from aqueous methanol in plates, m. p. 137° (Found : C, 67·5; H, 7·3. $C_{21}H_{26}O_4S$ requires C, 67·4; H, 7·0%).

The substance (XVI) (200 mg.) in tetrahydrofuran (15 c.c.) was reduced with lithium aluminium hydride (200 mg.) under reflux for 1 hr. After destruction of excess of reagent with dilute sulphuric acid, the product was recovered by evaporation of the organic layer. Crystallisation from ethyl acetate–light petroleum gave prisms (130 mg.), m. p. 127—128°, not depressed on admixture with *cis-syn*-$\Delta^{9(14)}$-dodecahydro-1 : 4-dihydroxyphenanthrene (IX).

The substance (XVI) (200 mg.) was heated under reflux for 2 hr. with 5% methanolic potassium hydroxide (20 c.c.). After cooling, dilution with water and recrystallisation of the precipated solid from light petroleum gave fine needles (140 mg.) of trans-anti-$\Delta^{9(14)}$-*dodecahydro*-

1-*hydroxy*-4-*oxophenanthrene* (XVII), m. p. 111—112° (Found: C, 76·2; H, 9·0. $C_{14}H_{20}O_2$ requires C, 76·2; H, 9·1%). Passage down a column of alkaline alumina in benzene–chloroform (4 : 1) solution failed to effect this stereoisomerisation, which was only partially effected by heating under reflux with 2% methanolic potassium hydroxide for 1 hr.

trans-anti-$\Delta^{9(14)}$-*Dodecahydro*-1 : 4-*dihydroxyphenanthrene* (XVIII*b*).—A solution of *trans-anti*-$\Delta^{9(14)}$-dodecahydro-1-hydroxy-4-oxophenanthrene (XVII) (87 mg.) in dry ether was heated under reflux with lithium aluminium hydride (100 mg.) for 1 hr. After destruction of excess of reagent with ethyl acetate and decomposition of the mixture with excess of dilute sulphuric acid, the ether layer was separated, washed with water, dried, and evaporated. Crystallisation of the solid residue from ethyl acetate gave *trans-anti*-$\Delta^{9(14)}$-dodecahydro-1 : 4-dihydroxyphenanthrene (XVIII*b*) (60 mg.), m. p. 194—195°, identical with a specimen prepared by an alternative route.

Catalytic Hydrogenation of trans-anti-$\Delta^{9(14)}$-*Dodecahydro*-1-*hydroxy*-4-*oxophenanthrene* (XVII).—(*a*) *trans-anti*-$\Delta^{9(14)}$-Dodecahydro-1-hydroxy-4-oxophenanthrene (170 mg.) was hydrogenated in methanol at atmospheric pressure and room temperature in presence of Adams's platinum oxide (50 mg.). Absorption of hydrogen was slow and appeared to cease entirely after about half the expected volume had been taken up. Removal of the catalyst and evaporation of the solvent gave a solid residue, which, on crystallisation from ethyl acetate–light petroleum, gave needles (63 mg.) of trans-anti-cis-*perhydro*-1-*hydroxy*-4-*oxophenanthrene* (XX*a*), m. p. (micro) 177—177·5° (Found: C, 75·6; H, 10·1. $C_{14}H_{22}O_2$ requires C, 75·6; H, 10·0%); oxidation of this compound (40 mg.) with chromium trioxide in acetic acid gave *trans-anti-cis*-perhydro-1 : 4-dioxophenanthrene (diketone D) (XIII), m. p. 107—109°, not depressed on admixture with an authentic specimen obtained as described below.

(*b*) *trans-anti*-$\Delta^{9(14)}$-Dodecahydro-1-hydroxy-4-oxophenanthrene (70 mg.) was hydrogenated in acetic acid (20 c.c.) at atmospheric pressure and room temperature in presence of Adams's platinum oxide until absorption ceased (1·5 hr.; 20 c.c.). After removal of the catalyst, evaporation of the solvent gave a solid residue, crystallising from ethyl acetate in fine needles, m. p. (micro) 208—210°, not depressed on admixture with a specimen of *trans-anti-cis*-perhydro-1 : 4-dihydroxyphenanthrene (XIX*b*), m. p. (micro) 211°, obtained as described below. Oxidation of this diol (XIX*b*) (60 mg.) in acetic acid (5 c.c.) with chromium trioxide (70 mg.) gave *trans-anti-cis*-perhydro-1 : 4-dioxophenanthrene (diketone D) (XIII) (30 mg.), m. p. 107—108°, not depressed on admixture with an authentic specimen (see below).

Stereoisomerisation of trans-anti-cis-*Perhydro*-1 : 4-*dioxophenanthrene* (*Diketone* D) (XIII) *by Alkaline Alumina*.—A solution of diketone D (400 mg.) in benzene was allowed to percolate down a column of alumina (8 g., Peter Spence & Sons, Ltd., type H) and the column was eluted with benzene (300 c.c.). Evaporation of the eluate and exhaustive fractional crystallisation of the residue from light petroleum, combined with hand-sorting of the different crystalline forms obtained in many fractions, gave *trans-syn-cis*- (diketone B) (V) (100 mg.), m. p. 115—116°, *cis-anti-cis*- (diketone C) (XII) (140 mg.), m. p. 138—139°, and unchanged *trans-anti-cis*-perhydro-1 : 4-dioxophenanthrene (diketone D) (XIII) (50 mg.), m. p. 109—110°, identical with authentic specimens.

Stereoisomerisation of cis-syn-$\Delta^{9(14)}$-*Dodecahydro*-1 : 4-*dioxophenanthrene* (I). trans-anti-$\Delta^{9(14)}$-*Dodecahydro*-1 : 4-*dioxophenanthrene* (XXI).—A solution of *cis-syn*-$\Delta^{9(14)}$-dodecahydro-1 : 4-dioxophenanthrene (1 g.) in benzene was allowed to percolate down a column of alkaline alumina (50 g., Peter Spence & Sons, Ltd., type H) and eluted with benzene. Evaporation of the eluate gave a solid residue (900 mg.), affording, after one recrystallisation from light petroleum, felted needles (600 mg.) of a stereoisomeric unsaturated diketone, namely *trans-anti*-$\Delta^{9(14)}$-dodecahydro-1 : 4-dioxophenanthrene (XXI), m. p. 139—140°, identical with that obtained in poor yield by reduction of *cis-syn*-$\Delta^{2:9(14)}$-decahydro-1 : 4-dioxophenanthrene (II) with zinc powder in boiling glacial acetic acid (Part I), or by boiling an acetic acid solution of *cis-syn*-$\Delta^{9(14)}$-dodecahydro-1 : 4-dioxophenanthrene (I). The substance (XXI) showed a medium-intensity band at 820 $cm.^{-1}$ in its infra-red absorption spectrum.

In a series of alkaline alumina stereoisomerisations of (I) carried out on a larger scale the yields were very variable; it was later found that a different specimen of alumina (Savory & Moore Ltd., " for chromatographic analysis ") gave more reproducible results on the larger scale (yields, 60—75%, with a ratio of compound to alumina of 1 : 20).

Reduction of trans-anti-$\Delta^{9(14)}$-*Dodecahydro*-1 : 4-*dioxophenanthrene* (XXI) *with Lithium Aluminium Hydride*. trans-anti-$\Delta^{9(14)}$-*Dodecahydro*-1 : 4-*dihydroxyphenanthrene* (XVIII*a*, *b*, *c*).—A solution of *trans-anti*-$\Delta^{9(14)}$-dodecahydro-1 : 4-dioxophenanthrene (2 g.) in anhydrous ether (200 c.c.) was added to lithium aluminium hydride (3 g.) in ether (200 c.c.), and the mixture was

heated under reflux for 2 hr., then cooled and decomposed with cold dilute sulphuric acid. A quantity of insoluble solid was left in suspension and was collected by filtration (A), and the ether layer, after being washed with water, was dried and evaporated, giving a solid (B). Crystallisation of solid (A) from ethanol–ethyl acetate gave fine needles (0·95 g.) of one stereoisomeric form (XVIII*a*) of trans-anti-$\Delta^{9(14)}$-*dodecahydro*-1 : 4-*dihydroxyphenanthrene*, m. p. 217—218° (Found, in a specimen dried at 100° in a high vacuum : C, 75·9; H, 9·9. $C_{14}H_{22}O_2$ requires C, 75·6; H, 10·0%).

The residue (B), together with the material recovered from the mother-liquors of the preceding crystallisation (total, 0·87 g.), was chromatographed in benzene on alumina (30 g.; Savory & Moore Ltd., deactivated by the addition of 6% of water). Elution with increasing strengths of chloroform in benzene gave, in the following order : (i) an unsaturated diol (80 mg.), m. p. 214—216° after crystallisation from ethyl acetate, identical with (XVIII*a*) (above); (ii) a stereoisomeric unsaturated *diol* (XVIII*b*) (80 mg.), m. p. 194—195° after crystallisation from ethyl acetate (Found : C, 75·6; H, 10·3%); (iii) a third stereoisomeric unsaturated *diol* (XVIII*c*) (150 mg.), m. p. 187—188° [depressed on admixture with (XVIII*b*)] after crystallisation from ethyl acetate (Found : C, 75·5; H, 10·0%).

trans-anti-trans-*Perhydro*-1 : 4-*dioxophenanthrene* (*Diketone E*) (XXIII) *and* trans-anti-trans-*Perhydro*-4-*hydroxy*-1-*oxophenanthrene* (XXII).—*trans-anti*-$\Delta^{9(14)}$-Dodecahydro-1 : 4-dioxophenanthrene (XXI) (7 g.), suspended in methanol (150 c.c.), was hydrogenated at atmospheric pressure and room temperature in presence of palladised strontium carbonate (2 g.). After approximately one mol. of hydrogen had been absorbed (4·5 hr.) the rate of uptake fell. Adams's platinum oxide (100 mg.) was then added and hydrogenation was continued as before, a further molecular proportion being absorbed in the next 4 hr. After removal of the catalyst and solvent, the solid residue was crystallised from ethyl acetate–light petroleum, giving woolly needles (2·45 g.) of trans-anti-trans-*perhydro*-4-*hydroxy*-1-*oxophenanthrene* (XXII), m. p. 138—140° (Found : C, 75·8; H, 10·0. $C_{14}H_{22}O_2$ requires C, 75·6; H, 10·0%). The *acetate*, obtained by the action of acetic anhydride–pyridine at room temperature or by heating with glacial acetic acid containing 1% of toluene-*p*-sulphonic acid, separated from aqueous methanol in colourless needles, m. p. 106—108° (Found : C, 72·4; H, 9·2. $C_{16}H_{24}O_3$ requires C, 72·7; H, 9·2%). The *toluene*-p-*sulphonate*, obtained by the action of toluene-*p*-sulphonyl chloride in dry pyridine, separated from aqueous methanol in needles, m. p. 142—143°, depressed on admixture with the starting material (Found : C, 66·7; H, 7·6. $C_{21}H_{28}O_4S$ requires C, 67·0; H, 7·5%).

The mother-liquors from the crystallisation of (XXII) were evaporated to dryness and the residue, dissolved in acetic acid (100 c.c.), was oxidised with chromium trioxide (3·0 g.). The product, recovered by addition of benzene and water and evaporation of the organic phase, was crystallised from light petroleum, giving fine needles (2 g.) of trans-anti-trans-*perhydro*-1 : 4-*dioxophenanthrene* (diketone E) (XXIII), m. p. 112—113° (Found : C, 76·3; H, 9·0. $C_{14}H_{20}O_2$ requires C, 76·2; H, 9·1%).

Attempts to interrupt the hydrogenation after one mol. of hydrogen had been absorbed gave mixtures from which pure products could not readily be separated, while the use of a palladium catalyst alone made hydrogenation unduly slow during the second stage.

Both diketone E (XXIII) and the hydroxy-ketone (XXII) were stable to treatment with alkaline alumina, and the latter was recovered unchanged after 2 hours' refluxing with 10% methanolic potassium hydroxide, after standing or refluxing with ethanolic sodium ethoxide, and after 15 minutes' refluxing with a solution of potassium *tert.*-butoxide in *tert.*-butanol. Diketone E (XXIII), which was, of course, not stable under these vigorous alkaline conditions, could be dissolved in cold concentrated sulphuric acid and largely recovered by rapid reprecipitation with water.

Interconversion of trans-anti-trans-*Perhydro*-1 : 4-*dioxophenanthrene* (XXIII) *and* trans-anti-trans-*Perhydro*-4-*hydroxy*-1-*oxophenanthrene* (XXII).—(*a*) *trans-anti-trans*-Perhydro-1 : 4-dioxophenanthrene (200 mg.) was shaken in methanol (20 c.c.) under hydrogen in the presence of Adams's platinum oxide (50 mg.) until absorption ceased (*ca.* 30 min.). Removal of the catalyst and evaporation of the solvent gave a solid, yielding on crystallisation from benzene–light petroleum fine needles (170 mg.), m. p. 140—141°, identical with other specimens of the hydroxy-ketone (XXII).

(*b*) *trans-anti-trans*-Perhydro-4-hydroxy-1-oxophenanthrene (50 mg.) in acetic acid (5 c.c.) was oxidised with chromium trioxide (30 mg., 2 equivs.) at room temperature overnight. Isolation in the usual way, using water and chloroform, gave a solid in almost quantitative yield, and recrystallisation from light petroleum afforded flat needles, m. p. 111—112°, identical with other specimens of the diketone (XXIII).

Conversion of trans-anti-trans-*Perhydro*-4-*hydroxy*-1-*oxophenanthrene* (XXII) *into* 1-*Methylphenanthrene.*—*trans-anti-trans*-Perhydro-4-hydroxy-1-oxophenanthrene (2 g.) in benzene (100 c.c.) was added dropwise to a refluxing solution of methylmagnesium iodide (from 2·5 g. of magnesium) in benzene (100 c.c.), and the mixture was heated under reflux for 3·5 hr. After cooling and decomposition of the mixture with excess of dilute sulphuric acid, the product, which was rather insoluble, was isolated by the addition of chloroform and evaporation of the organic phase. Crystallisation of the residue from ethyl acetate afforded fine needles (1·67 g.) of trans-anti-trans-*perhydro*-1 : 4-*dihydroxy*-1-*methylphenanthrene*, m. p. 179—181° (Found, in a specimen dried at 100°/0·1 mm. for 2 hr.: C, 75·6; H, 11.0. $C_{15}H_{26}O_2$ requires C, 75·6; H, 11·0%). The substance (1·5 g.) was dehydrated and dehydrogenated (in the manner described above for *trans-syn-cis*-perhydro-1 : 4-dihydroxy-4-methylphenanthrene) to give 1-methylphenanthrene (0·6 g.), m. p. 119—120° (styphnate, m. p. 149—150°), identical with specimens prepared by alternative routes.

Catalytic Hydrogenation of trans-anti-$\Delta^{9(14)}$-*Dodecahydro*-1 : 4-*dihydroxyphenanthrene* (XVIII*a*). trans-anti-trans-*Perhydro*-1 : 4-*dihydroxyphenanthrene* (XXIV*a*).—A solution of *trans-anti*-$\Delta^{9(14)}$-dodecahydro-1 : 4-dihydroxyphenanthrene (XVIII*a*) (300 mg.) in methanol (30 c.c.) was shaken in hydrogen in presence of freshly reduced 2% palladium–strontium carbonate (500 mg.). After 71 hr. the catalyst was removed and evaporation of the solvent gave a solid residue. Three recrystallisations from ethyl acetate gave rosettes of needles of trans-anti-trans-*perhydro*-1 : 4-*dihydroxyphenanthrene* (XXIV*a*), m. p. (micro) 190—191° (Found: C, 74·9; H, 10·6. $C_{14}H_{24}O_2$ requires C, 75·0; H, 10·8%); the m. p. was depressed on admixture with a stereoisomeric *trans-anti-trans*-perhydro-1 : 4-dihydroxyphenanthrene (XXIV*b*), m. p. (micro) 194—195°. Oxidation of (XXIV*a*) (130 mg.) in acetic acid (10 c.c.) with chromium trioxide (140 mg.) gave *trans-anti-trans*-perhydro-1 : 4-dioxophenanthrene (diketone E) (XXIII), m. p. 110—112°, not depressed on admixture with a specimen prepared as described above.

trans-anti-cis-*Perhydro*-1 : 4-*dioxophenanthrene* (*Diketone D*) (XIII), trans-anti-cis-*Perhydro*-1 : 4-*dihydroxyphenanthrenes* (XIX*a*, *b*, *c*), *and* trans-anti-trans-*Perhydro*-1 : 4-*dihydroxyphenanthrene* (XXIV*b*).—(*a*) *trans-anti*-$\Delta^{9(14)}$-Dodecahydro-1 : 4-dioxophenanthrene (XXI) (2 g.) in glacial acetic acid (50 c.c.) was hydrogenated in presence of Adams's platinum oxide (100 mg.) at room temperature and atmospheric pressure until slightly more than three mols. of hydrogen had been absorbed. After removal of the catalyst, chromium trioxide (2·5 g.) in water (10 c.c.) was added and the mixture was set aside overnight. Isolation of the product with the aid of benzene and crystallisation from light petroleum gave fine needles (0·72 g.) of trans-anti-cis-*perhydro*-1 : 4-*dioxophenanthrene* (diketone D) (XIII), m. p. 108—109°, depressed on admixture with the stereoisomeric diketones (diketones A, B, and E) of similar m. p. (Found: C, 76·5; H, 9·2. $C_{14}H_{20}O_2$ requires C, 76·2; H, 9·1%). In one experiment a small quantity of *trans-anti-trans*-perhydro-1 : 4-dioxophenanthrene (diketone E) (XXIII) was isolated by fractional crystallisation of material remaining in the mother liquors.

(*b*) The mixture of diols resulting from the reduction, as in (*a*), of *trans-anti*-$\Delta^{9(14)}$-dodecahydro-1 : 4-dioxophenanthrene (XXI) (2 g.) was chromatographed on partly deactivated alumina (100 g., Savory & Moore Ltd.; deactivated by addition of 6% of water) in benzene chloroform (9 : 1). Careful elution with increasing concentrations of chloroform in benzene gave four distinct saturated diols. Repeated chromatography of the combined intermediate fractions and mother-liquors gave further quantities of the same substances. The products, listed in the order of elution, were related to *trans-anti-cis*- (diketone D) (XIII) and *trans-anti-trans*-perhydro-1 : 4-dioxophenanthrene (diketone E) (XXIII) by oxidation with chromium trioxide in acetic acid in the usual way. A total yield of 67% of pure saturated diols (all crystallised from ethyl acetate) was obtained: (i) trans-anti-cis-*perhydro*-1 : 4-*dihydroxyphenanthrene* (XIX*a*) (2%), clusters of needles, m. p. (micro) 184—185° (Found: C, 75·0; H, 10·8. $C_{14}H_{24}O_2$ requires C, 75·0; H, 10·8%); oxidation gave diketone D: (ii) trans-anti-cis-*perhydro*-1 : 4-*dihydroxyphenanthrene* (XIX*b*) (13%), fine needles, m. p. (micro) 211° (Found: C, 74·9; H, 11·0%); oxidation gave diketone D: (iii) trans-anti-trans-*perhydro*-1 : 4-*dihydroxyphenanthrene* (XXIV*b*) (18%), woolly needles, m. p. (micro) 194—195° (Found: C, 74·9; H, 10·8%); oxidation gave diketone E: (iv) trans-anti-cis-*perhydro*-1 : 4-*dihydroxyphenanthrene* (XIX*c*) (34%), plates, m. p. (micro) 201° (Found: C, 74·8; H, 11·0%); oxidation gave diketone D.

Reduction of trans-anti-cis-*Perhydro*-1 : 4-*dioxophenanthrene* (*Diketone D*) (XIII) *to* trans-anti-cis-*Perhydro*-1(?)-*hydroxy*-4(?)-*oxophenanthrene* (XX*b*).—*trans-anti-cis*-Perhydro-1 : 4-dioxophenanthrene (400 mg.) in methanol (20 c.c.) was hydrogenated at room temperature and pressure in the presence of Adams's platinum oxide (50 mg.). Uptake of hydrogen ceased after

the absorption of rather more than one mol. in 15 min. On removal of the catalyst and solvent the residue crystallised from benzene–light petroleum giving clusters of needles (330 mg.) of trans-anti-cis-*perhydro*-1(?)-*hydroxy*-4(?)-*oxophenanthrene* (XX*b*), m. p. 144—145° (Found: C, 75·9; H, 10·2. $C_{14}H_{22}O_2$ requires C, 75·6; H, 10·0%). Oxidation of this hydroxy-ketone with chromium trioxide in acetic acid regenerated diketone D. The substance was recovered unchanged after 2·5 hours' heating with 10% alcoholic potassium hydroxide.

Oxidation of cis-syn-cis-*Perhydro*-1 : 4-*dihydroxyphenanthrene* (VIII) *with the Chromium Trioxide–Pyridine Reagent.* cis-syn-cis-*Perhydro*-1-*hydroxy*-4-*oxophenanthrene* (XXIX).—*cis-syn-cis*-Perhydro-1 : 4-dihydroxyphenanthrene (1·0 g.) in pyridine (15 c.c.) was oxidised with the chromium trioxide–pyridine reagent (from 1·5 g. of chromium trioxide, 4·5 equivs.) in pyridine (15 c.c.) at room temperature for 4 hr. The mixture was then poured into water and extracted five times with chloroform, frequent filtration being necessary to remove the flocculent brown matter that separated. The combined chloroform extracts were washed free from pyridine with dilute sulphuric acid, then with water and dilute sodium hydrogen carbonate, dried, and evaporated. The resulting viscous brown oil was extracted several times with boiling light petroleum, and a small brown residue was discarded. On cooling, the combined almost colourless extracts deposited a mixture of small dense prisms and flocculent woolly needles, and these were hand-sorted. The woolly needles had an indeterminate m. p., not improved by recrystallisation, and they were combined with material recovered from the mother-liquors for subsequent chromatography. The prisms, on recrystallisation from ethyl acetate–light petroleum, afforded cis-syn-cis-*perhydro*-1-*hydroxy*-4-*oxophenanthrene* (XXIX) in the form of rods (150 mg.), m. p. 123—124° (Found: C, 75·9; H, 10·1. $C_{14}H_{22}O_2$ requires C, 75·6; H, 10·0%).

The uncharacterised material (0·77 g.) was dissolved in benzene–light petroleum (1 : 1) and chromatographed on a column of alkaline alumina (30 g., Peter Spence & Sons, Ltd., type H), and elution with benzene and benzene containing a progressively increasing proportion of chloroform gave first a diketone fraction and then a hydroxy-ketone fraction.

The diketone fraction (120 mg.), on crystallisation from light petroleum, gave a mixture of two crystal forms, which, on repeated hand-sorting and recrystallisation, afforded *trans-syn-cis*-perhydro-1 : 4-dioxophenanthrene (diketone B) (V), m. p. 115—116°, and *cis-anti-cis*-perhydro-1 : 4-dioxophenanthrene (diketone C) (XII), m. p. 141°, identical with specimens obtained previously. These were presumably derived from the alkaline rearrangement of *cis-syn-cis*-perhydro-1 : 4-dioxophenanthrene (diketone A) (III), present originally in the oxidation product.

The hydroxy-ketone fraction (350 mg.), on crystallisation from ethyl acetate–light petroleum, afforded *trans-anti-cis*-perhydro-1-hydroxy-4-oxophenanthrene (XX*a*) (130 mg.) in the form of rectangular plates, m. p. 172—173°, identical with specimens obtained by an alternative route; this substance was obviously derived from the *cis-syn-cis*-compound (XXIX), partly isolated above by direct crystallisation from the reaction product (see following experiment). The mother-liquors on concentration deposited rosettes of fine needles, m. p. *ca.* 125—130°, which could not be further purified by repeated crystallisation, but the m. p. was raised on admixture with *trans-syn-cis*-perhydro-4-hydroxy-1-oxophenanthrene (VI), m. p. 141°; out of seventeen prominent bands in the 900—1300 cm.$^{-1}$ region of the infra-red absorption spectrum of the material, m. p. *ca.* 125—130°, fifteen were also found in that of (VI) and three in that of (XX*a*). *trans-syn-cis*-Perhydro-4-hydroxy-1-oxophenanthrene (VI), if present, could have been derived from a *cis-syn-cis*-precursor (IV), present in the original oxidation product, on passage over alkaline alumina.

Stereoisomerisation of cis-syn-cis-*Perhydro*-1-*hydroxy*-4-*oxophenanthrene* (XXIX). trans-anti-cis-*Perhydro*-1-*hydroxy*-4-*oxophenanthrene* (XX*a*).—A solution of *cis-syn-cis*-perhydro-1-hydroxy-4-oxophenanthrene (50 mg.) in methanolic potassium hydroxide (10 c.c. of 5%) was heated under reflux for 1 hr. After partial removal of solvent by distillation, addition of water gave an almost quantitative yield of *trans-anti-cis*-perhydro-1-hydroxy-4-oxophenanthrene (XX*a*) in the form of lustrous plates, m. p. 171—172°, not depressed on admixture with specimens obtained by other routes.

Oppenauer Oxidation of cis-syn-cis-*Perhydro*-1 : 4-*dihydroxyphenanthrene* (VIII).—A solution of *cis-syn-cis*-perhydro-1 : 4-dihydroxyphenanthrene (0·9 g.) in benzene (50 c.c.) containing *cyclo*hexanone (10 c.c.) was heated under reflux with aluminium *iso*propoxide (1·0 g.) for 7 hr. After cooling, water (2 c.c.) was added and the precipitated alumina was collected. The filtrate was evaporated under reduced pressure, finally at 100°/1 mm., and the residual oil was taken up in hot light petroleum. A small quantity of crystalline material separated on pro-

longed standing, but this had an indefinite m. p., and could not be further purified on recrystallisation. The entire reaction product (0·83 g.) was then chromatographed in benzene–light petroleum (1 : 1) on alkaline alumina (30 g., Peter Spence & Sons, Ltd., type H). Elution with benzene containing a progressively increasing proportion of chloroform afforded a diketone fraction followed by a hydroxy-ketone fraction.

The diketone fraction (230 mg.) was shown to be a mixture of *trans-syn-cis*- (diketone B) (V) and *cis-anti-cis*-perhydro-1 : 4-dioxophenanthrene (diketone C) (XII), by crystallisation and hand-sorting as described above.

The hydroxy-ketone fraction (250 mg.), on recrystallisation, afforded rectangular plates (200 mg.) of *trans-anti-cis*-perhydro-1-hydroxy-4-oxophenanthrene (XX*a*), m. p. 172—173°, not depressed on admixture with specimens obtained by other routes. No further crystalline material could be obtained from the mother-liquors.

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Substituted Fluoren-9-ols.

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The synthesis of 3-nitrofluorenone reported by Ray and Barrick (*J. Amer. Chem. Soc.*, 1948, **70**, 1493) has been revised. 2-Methyl-, 3-methyl-, 2-methoxy-, 3-methoxy,- 2-hydroxy-, 2-amino-, and 3-nitro-fluoren-9-ol have been prepared by reduction of the corresponding fluorenones with aluminium *iso*propoxide. A form of 9-phenylfluoren-9-ol having m. p. 85° (lit., 107°) has been obtained.

A number of fluoren-9-ols, substituted with groups of different electronic characteristics, have been prepared for use in the syntheses of phenanthridines to be described (Arcus and Coombs, *J.*, 1954, in the press).

Fluorenones.—2-Methyl-, 3-methyl-, and 3-methoxy-fluorenones have been obtained by known procedures.

The reduction of 2-nitro- to 2-amino-fluorenone is conveniently effected by stannous chloride. This amine was converted into 2-hydroxy- and hence into 2-methoxy-fluorenone by known methods.

A synthesis of 3-nitrofluorenone has been described by Ray and Barrick (*J. Amer. Chem. Soc.*, 1948, **70**, 1493); it consists of six stages: (i) conversion of 2-aminodiphenyl into its toluene-*p*-sulphonyl derivative; (ii) nitration of this at position 5; (iii) hydrolysis of the toluene-*p*-sulphonyl group; (iv) conversion of the amine into 2-cyano-5-nitrodiphenyl by a Sandmeyer reaction; (v) hydrolysis to 5-nitrodiphenyl-2-carboxylic acid; (vi) ring closure with sulphuric acid, yielding 3-nitrofluorenone. Ray and Barrick's procedures are effective for stages (i), (iii), (iv, modified), and (vi); those for stages (ii) and (v) proved unsatisfactory. Nitration, with fuming nitric–acetic acid according to these authors, gave an explosive reaction from the product of which the 5-nitro-derivative could not be isolated. Further, contrary to Ray and Barrick's statement, nitration with dilute nitric acid by Bell's method (*J.*, 1928, 2774) proceeds satisfactorily; 5-nitro-2-toluene-*p*-sulphonamidodiphenyl was obtained in 79% yield. Hydrolysis in stage (v) with 50% sulphuric acid according to Ray and Barrick gave much tar and poor yields of the carboxylic acid; hydrolysis with aqueous acetic–sulphuric acid (Jones and Braker, U.S.P. 1,922,205) is effective.

Fluoren-9-ols.—Reduction of the corresponding fluorenones with aluminium *iso*propoxide in hot *iso*propanol gave the following fluoren-9-ols in the stated yields: 2-methyl-

(80%), 3-methyl- (84%), 2-methoxy- (71%), 3-methoxy- (71%), 2-hydroxy- (50%), 2-amino- (69%), 3-nitro- (86%). The new fluorenols have been converted into the corresponding 9-acetoxyfluorenes; 9-chloro-2-methoxy-, 9-chloro-2-nitro-, and 9-chloro-3-nitrofluorene have been prepared.

9-Methyl- and 9-benzyl-fluoren-9-ol were obtained from the known reaction of fluorenone with, respectively, methylmagnesium iodide and benzylmagnesium chloride; the interaction of phenylmagnesium bromide with fluorenone added (*a*) in benzene–ether solution, (*b*) as the powdered solid according to the original preparation by Ullmann and von Wurstemberger (*Ber.*, 1904, **37**, 73), yielded in each instance 9-phenylfluoren-9-ol, m. p. 85°. The above authors, also Williamson, Anderson, and Watts (*J. Amer. Chem. Soc.*, 1943, **65**, 49), record m. p. 107°. On reaction with hydrazoic and sulphuric acids, the fluorenol, m. p. 85°, gave 9-phenylphenanthridine in 94% yield (Arcus and Coombs, *loc. cit.*); further, it yielded 9-chloro-9-phenylfluorene having m. p. 78°, a value identical with that recorded by Ullmann *et al.* and by Williamson *et al.* for this compound prepared from the higher-melting fluorenol. The two forms of the fluorenol appear, therefore, to be structurally identical; no geometrical isomers (due, *e.g.*, to folding) were apparent on inspection of a C.R.L.-Catalin model of 9-phenylfluoren-9-ol. The compound is concluded to be dimorphic.

Experimental

M. p.s are corrected.

Fluorenones.—By the use of Ritchie's procedures (*J. Proc. Roy. Soc., N.S.W.*, 1946, **80**, 33) there have been prepared, successively, 5-methyl-2 : 3-diphenylindole (49·5 g.), m. p. 155—156°, 1-acetyl-5-methyl-2 : 3-diphenylindole (46 g.), m. p. 175—177°, 2-amino-5-methylbenzophenone (22 g.), m. p. 60—61°, and 2-methylfluorenone [9·2 g., from light petroleum (b. p. 40—60°)], yellow needles, m. p. 91—92°. For these compounds, respectively, Ritchie records m. p. 156°, 176°, 63°, 92°.

2-Amino-4′-methylbenzophenone (10·7 g., m. p. 92°; *Org. Synth.*, 1952, **32**, 8) was converted into 3-methylfluorenone [4·5 g., from light petroleum (b. p. 40—60°)], yellow prisms, m. p. 68°, by the method of Ullmann and Mallet (*Ber.*, 1898, **31**, 1694), who record m. p. 66·5°.

2-Nitrofluorene (30 g.; m. p. 157—158°; *Org. Synth.*, 1933, **13**, 74) yielded 2-nitrofluorenone (27 g., from xylene), yellow leaflets, m. p. 220—221°, on oxidation according to Diels (*Ber.*, 1901, **34**, 1760), who records m. p. 222—223°. 2-Nitrofluorenone (100 g.), stannous chloride ($SnCl_2,2H_2O$; 400 g.), concentrated hydrochloric acid (400 ml.), and ethanol (200 ml.) were boiled together under reflux for 6 hr., and then cooled. The insoluble tin complex was collected and decomposed with an excess of 2N-sodium hydroxide. Crystallisation of the base from hot xylene gave permanganate-coloured needles of 2-aminofluorenone (68 g.), m. p. 158°. Diels (*loc. cit.*), who used ammonium sulphide as the reducing agent, records m. p. 160°.

2-Aminofluorenone (66 g.) was converted into 2-hydroxyfluorenone (61 g.), red needles, m. p. 206—208°, by the procedure of Diels (*loc. cit.*), who records m. p. 206—207°.

2-Hydroxyfluorenone (55 g.) gave 2-methoxyfluorenone (53·5 g.), orange needles, m. p. 75—76°, on methylation according to Werner and Gross (*Annalen*, 1902, **322**, 168), who record m. p. 77—78°.

By the use of Ullmann and Bleier's procedures (*Ber.*, 1902, **35**, 4273), *N*-toluene-*p*-sulphonylanthranilic acid (45 g.) was successively converted into 4-methoxy-2′-toluene-*p*-sulphonamidobenzophenone, 2-amino-4′-methoxybenzophenone sulphate, and 3-methoxyfluorenone [11·1 g., from light petroleum (b. p. 60—80°)], yellow prisms, m. p. 99—100°. The above authors record m. p. 99°.

A suspension of 2-toluene-*p*-sulphonamidodiphenyl (200 g.; m. p. 99—100°) in water (2 l.) and concentrated nitric acid (200 ml.) was stirred at 100° for 9 hr.; the yellow oil became converted into a flocculent orange solid which was collected and crystallised from glacial acetic acid (750 ml.); it yielded 5-nitro-2-toluene-*p*-sulphonamidodiphenyl (160 g., 79%), orange needles, m. p. 168—169°. The procedure is adapted from that applied to 1 g. of sulphonamide by Bell (*loc. cit.*), who records m. p. 169°. Nitration of the sulphonamide (78 g.) by Ray and Barrick's method (*loc. cit.*) was at first tried: when the temperature reached 70° a reaction of explosive violence occurred. Reaction was again violent in an experiment on one-third the scale. No pure compound was isolated.

5-Nitro-2-toluene-*p*-sulphonamidodiphenyl (570 g.) was hydrolysed to 2-amino-5-nitrodiphenyl (240 g.), m. p. 125°, which (220 g.) was converted into 2-cyano-5-nitrodiphenyl (120 g.), m. p. 133—135°, by Ray and Barrick's procedures, except that sodium cuprocyanide was prepared according to *Org. Synth.*, Coll. Vol. I, 2nd Edn., pp. 170, 514. This nitrile (118 g.), hydrolysed by Jones and Braker's method (*loc. cit.*), gave 5-nitrodiphenyl-2-carboxylic acid (89 g.), m. p. 180°. Ring closure of this compound by the procedure of Ray and Barrick yielded 3-nitrofluorenone (60·5 g., from glacial acetic acid), yellow needles, m. p. 235°. Recrystallisation from glacial acetic acid, from pyridine, and from ethanol did not raise the m. p.; the above authors record m. p. 235—236°, 239—240° (corr.), and Nunn, Schofield, and Theobald (*J.*, 1952, 2797) record m. p. 232—233° (uncorr.).

Fluoren-9-ols.—Aluminium isopropoxide reductions. The fluorenone was heated, under reflux for the stated time, with a solution of aluminium *iso*propoxide prepared from aluminium turnings and *iso*propanol (0·4 g. and 12 ml., respectively, to 1 g. of fluorenone). The mixture

Fluorenone	2-Me	3-Me	2-MeO	3-MeO	2-HO	2-NH_2	3-NO_2
Weight (g.)	5·0	4·5	40·0	7·7	2·0	16·0	20·0
Time (min.)	180	120	120	180	45 *	5 *	30 *

* Longer reaction times gave lower yields.

was poured into ice-cold N-sulphuric acid (20 ml. to 3 ml. of *iso*propanol), and the solid product was collected, washed, dried, and recrystallised.

9-Acetoxyfluorenes were prepared by heating the fluorenols with acetic anhydride and dry pyridine (respectively 1 ml. and 5 ml. to 1 g. of fluorenol) for 3 hr. on a steam-bath.

9-Chlorofluorenes were prepared by warming the fluorenols with thionyl chloride (5 ml. to 1 g. of fluorenol) until evolution of hydrogen chloride was complete; excess of thionyl chloride was removed *in vacuo*, and the product was recrystallised.

Exceptions to these procedures are recorded below. There were obtained:

2-*Methylfluoren*-9-*ol* [4·0 g., from light petroleum (b. p. 60—80°)], needles, m. p. 143—144° (Found: C, 85·65; H, 6·25. $C_{14}H_{12}O$ requires C, 85·7; H, 6·15%). It (1·0 g.) yielded 9-*acetoxy*-2-*methylfluorene* (1·0 g., from ethanol), needles, m. p. 114—115° (Found: C, 80·95; H, 6·2. $C_{16}H_{14}O_2$ requires C, 80·65; H, 5·9%).

3-*Methylfluoren*-9-*ol* [3·8 g., from light petroleum (b. p. 60—80°)], needles, m. p. 144—145° (admixture with 2-methylfluoren-9-ol depressed the m. p. by 20°) (Found: C, 85·8; H, 6·0%). It (1·0 g.) gave 9-*acetoxy*-3-*methylfluorene* (0·75 g., from ethanol), plates, m. p. 90° (Found: C, 80·6; H, 6·1%).

2-*Methoxyfluoren*-9-*ol* [28·5 g.; from benzene; the solution was boiled with charcoal (1 g.)], buff prisms, m. p. 160° (Found: C, 79·4; H, 5·95. $C_{14}H_{12}O_2$ requires C, 79·25; H, 5·7%). It (1·5 g.) gave 9-*acetoxy*-2-*methoxyfluorene* (1·6 g., from ethanol), orange tablets, m. p. 82—83° (Found: C, 75·75; H, 5·8. $C_{16}H_{14}O_3$ requires C, 75·6; H, 5·55%). The fluorenol (10·0 g.) yielded 9-*chloro*-2-*methoxyfluorene* [8·0 g., from light petroleum (b. p. 40—60°)], yellow platelets, m. p. 98·5—99·5° (Found: C, 72·6; H, 4·85; Cl, 15·25. $C_{14}H_{11}OCl$ requires C, 72·9; H, 4·8; Cl, 15·4%).

3-*Methoxyfluoren*-9-*ol* [5·5 g., from light petroleum (b. p. 100—110°)], leaflets, m. p. 120° (Found: C, 78·6, 78·6; H, 5·75, 5·8%). It (0·5 g.) gave 9-*acetoxy*-3-*methoxyfluorene* (0·4 g., from ethanol), m. p. 126—127° (Found: C, 75·55; H, 5·7%).

2-*Hydroxyfluoren*-9-*ol* (1·0 g.; the product from the reduction was reprecipitated from its filtered solution in 2N-sodium hydroxide, and crystallised from glacial acetic acid), golden needles, m. p. 188—189° (Found: C, 78·5; H, 5·15. $C_{13}H_{10}O_2$ requires C, 78·75; H, 5·1%). It (0·15 g.) was heated for 4 hr. with a treble quantity of reagents and yielded 2 : 9-*diacetoxyfluorene* (0·1 g., from 50 % ethanol), prisms, m. p. 106° (Found: C, 72·35; H, 4·95. $C_{17}H_{14}O_4$ requires C, 72·35; H, 5·0%).

The solution from the reduction of 2-aminofluorenone was poured into ice-cold 2·5N-sodium hydroxide (1 l.); the product was reprecipitated from its solution in N-hydrochloric acid. It yielded 2-aminofluoren-9-ol (11 g., from ethanol), leaflets, m. p. 197—198°; Diels (*Ber.*, 1901, 34, 1767) obtained this compound, m. p. 196°, by reducing 2-nitrofluorenone with zinc dust.

2-Nitrofluorenone (22·4 g.) gave 2-nitrofluoren-9-ol (18·7 g.), m. p. 128—129°, on reduction with aluminium *iso*propoxide according to Friedler (Ph.D. Thesis, London, 1952), who records the same m. p. for this compound; it (13·2 g.) yielded 9-*chloro*-2-*nitrofluorene* (10·5 g., from benzene), yellow columns, m. p. 141° (Found: C, 63·6; H, 3·25; N, 5·4; Cl, 14·45. $C_{13}H_8O_2NCl$ requires C, 63·55; H, 3·3; N, 5·7; Cl, 14·45%).

3-Nitrofluorenone was added in suspension in benzene (200 ml.) to the reagent prepared from 100 ml. of *iso*propanol; there was obtained *3-nitrofluoren-9-ol* (17·3 g., from benzene), needles, m. p. 156° (Found: C, 68·45; H, 4·1; N, 6·2. $C_{13}H_9O_3N$ requires C, 68·7; H, 4·0; N, 6·2%). It (1·0 g.), heated under reflux for 5 hr. with acetic anhydride (20 ml.) and glacial acetic acid (20 ml.), gave *9-acetoxy-3-nitrofluorene* (0·9 g., from ethanol), yellow needles, m. p. 130° (Found: C, 66·95; H, 3·85; N, 5·45. $C_{15}H_{11}O_4N$ requires C, 66·9; H, 4·1; N, 5·2%). The fluorenol (1·2 g.) yielded *9-chloro-3-nitrofluorene* (0·55 g., from benzene), needles, m. p. 150—151° (Found: C, 63·5; H, 3·3; Cl, 14·8%).

9-Methylfluoren-9-ol (7·2 g., from benzene–ether), needles, m. p. 175°, and 9-benzylfluoren-9-ol [2·7 g., from benzene–light petroleum, b. p. 40—60°)], tablets, m. p. 140—141°, were prepared by the interaction of fluorenone (8·0 g. for each) with methylmagnesium iodide and benzylmagnesium chloride by the method described below. For these fluorenols Ullmann (*Ber.*, 1905, **38**, 4107) records m. p. 174·5° and m. p. 139°.

To a stirred solution of phenylmagnesium bromide (from magnesium, 1·5 g., bromobenzene, 6·6 ml., and ether, 40 ml.) was added, during ½ hr., a solution of fluorenone (10·0 g.) in benzene–ether (20 ml. each). The mixture was heated for an hour on a steam-bath and added to ice and ammonium chloride; the benzene–ether solution was dried (Na_2SO_4) and concentrated to 30 ml., and light petroleum (b. p. 40—60°; 100 ml.) was added. There separated rhombs (11·1 g.), m. p. 73—75°, which (2·00 g.) lost solvent and attained constant weight (1·74 g.) during 30 min. at 120°; the resulting colourless melt solidified on cooling, to crystalline 9-phenylfluoren-9-ol, m. p. 85° (Found: C, 88·0; H, 5·4. Calc. for $C_{19}H_{14}O$: C, 88·35; H, 5·45%). This compound, on recrystallisation from benzene, gave rhombs, m. p. 74—75° alone or when mixed with the substance of m. p. 73—75°, above. On recrystallisation from carbon tetrachloride, the fluorenol, m. p. 85°, gave prisms m. p. 80—84°, which effloresced in air; after 24 hr. the white powder again melted at 85°, alone or in admixture with the analysed specimen. 9-Phenylfluoren-9-ol was also prepared by Ullmann and von Wurstemberger's method (*loc. cit.*); it separated from light petroleum (b. p. 60—80°), containing benzene, as rhombs, m. p. 75° alone or when mixed with the similar material from the above preparation. Solvent was removed by heating the substance at 120° for 1 hr.; the product then had m. p 85—86° alone and when mixed with the analysed specimen. The above authors obtained 9-phenylfluoren-9-ol, m. p. 107°, which, when recrystallised from carbon tetrachloride, formed solvated crystals, m. p. 85—88°; they also obtained a solvated fluorenol from benzene (m. p. unstated).

Phosphorus pentachloride (2·2 g.) was added to a solution of 9-phenylfluoren-9-ol (2·6 g.; m. p. 85°) in benzene (25 ml.); after 10 min. the solution was boiled under reflux for 5 min., then cooled and shaken with ice. The product (2·8 g.) from the benzene layer yielded 9-chloro-9-phenylfluorene [0·5 g., from light petroleum (b. p. 40—60°)], tablets, m. p. 78°. Ullmann and von Wurstemberger (*loc. cit.*), also Williamson, Anderson, and Watts (*loc. cit.*), obtained 9-chloro-9-phenylfluorene, m. p. 78—79°, from 9-phenylfluoren-9-ol having m. p. 107°.

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Constituents of "Cortex Piscidiae Erythrinae." Part II. The Synthesis of O-Methylpiscidic Acid.*

By A. L. J. Buckle, Alexander McGookin, and Alexander Robertson.

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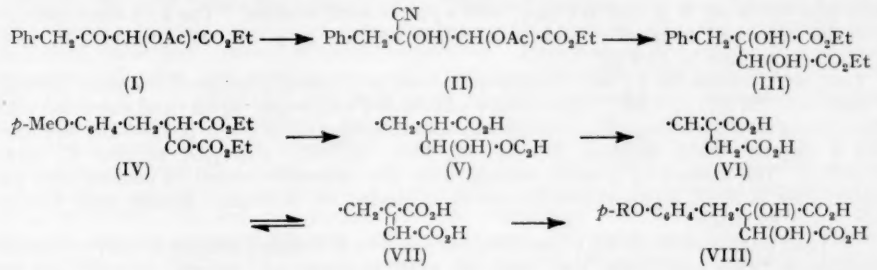
On being heated *p*-methoxybenzylidenesuccinic acid gave a poor yield of *p*-methoxybenzylmaleic acid which on hydroxylation with osmium tetroxide in the presence of pyridine furnished a racemate of *p*-methoxybenzyltartaric acid. Resolution of this compound gave (+)-*p*-methoxybenzyltartaric acid, identical with natural *O*-methylpiscidic acid.

In Part I (*J.*, 1948, 257) piscidic acid, from "Cortex Piscidiae Erythrinae," was shown to be a (+)-*p*-hydroxybenzyltartaric acid (VIII; R = H) and this has now been confirmed by the synthesis of (+)-*O*-methylpiscidic acid (VIII; R = Me). Of the several possible routes for the synthesis of tartaric acids of this type (VIII) two were simultaneously examined, *viz.*, (*a*) the preparation and hydroxylation of the requisite maleic acid and (*b*) the addition of hydrogen cyanide to ketonic esters of type (I) followed by hydrolysis of the resulting cyanohydrin, a method which would be expected to furnish the two racemates possible with tartaric acids of the piscidic acid type. In model experiments by route (*b*) the acetoxylation of ethyl γ-phenylacetoacetate with lead tetra-acetate furnished ethyl α-acetoxy-γ-phenylacetoacetate (I), the orientation of which was confirmed by its preparation, albeit in poor yield, from ethyl α-diazo-γ-phenylacetoacetate, formed by the interaction of phenylacetyl bromide and ethyl diazoacetate. On treatment with alcoholic hydrogen chloride the cyanohydrin (II) from (I) was converted into ethyl benzyltartrate (III) which was separated by fractional crystallisation into the two racemic forms, characterised by conversion into the corresponding diamides.



Because of the meagre yields obtained in the cyanohydrin route our efforts were concentrated on route (*a*). The oxidation of citraconic acid with osmium tetroxide and sodium chlorate furnished one of the racemates of methyltartaric acid obtained from ethyl α-acetoxyacetoacetate by the cyanohydrin method † (cf. Schmidt and Perkow, *Chem. Ber.*, 1950, **83**, 484) but attempts to convert phenylmaleic acid into phenyltartaric acid with the osmium tetroxide–sodium chlorate reagent were unsuccessful. By the osmium tetroxide–pyridine procedure of Craigie, Marchand, and Wannowius (*Annalen*, 1942, **550**, 99), however, phenylmaleic acid was hydroxylated to a racemate of phenyltartaric acid. The phenylmaleic acid for this was prepared by dehydrating the mixed racemates of phenylmalic acid which were obtained by the reduction of ethyl phenyloxaloacetate with aluminium amalgam, a method superior to Alexander's (*Annalen*, 1890, **258**, 76). Similarly the condensation of ethyl β-*p*-methoxyphenylpropionate with ethyl oxalate furnished the keto-ester (IV) and this on reduction gave ethyl α-hydroxy-β-*p*-methoxybenzylsuccinate which was hydrolysed

* Part I, *J.*, 1948, 257.

† Schmidt and Perkow's paper (*Chem. Ber.*, 1950, **83**, 484) appeared after the experimental work on the cyanohydrin method had been completed in 1949; the results were presented in a Thesis for Degree of Master of Science by Dr. A. L. J. Buckle in 1949. A. R.

to the malic acid (V). This was separated into two racemic forms but attempts to convert it into the maleic acid (VII) or its anhydride were unsuccessful. With warm acetic anhydride alone or in ether, phosphoric oxide, or phosphoryl chloride, either racemate gave only *p*-methoxybenzylidenesuccinic anhydride, identical with a specimen prepared by the condensation of *p*-anisaldehyde and ethyl succinate with subsequent hydrolysis of the ester and dehydration of the resulting acid; in agreement with the structure (VI) the ultra-violet absorption spectrum of this acid closely resembled that of *p*-methoxycinnamic acid. Similarly, the dehydrogenation of *p*-methoxybenzylsuccinic acid with *N*-bromosuccinimide in the presence of a little benzoyl peroxide by the method of Miller, Staley, and Mann (*J. Amer. Chem. Soc.*, 1949, **71**, 374) gave only the benzylidenesuccinic acid (VI). The Kreb's heart muscle dehydrogenase, which converts succinic acid into maleic acid (*Biochem. J.*, 1937, **31**, 2095), did not attack *p*-methoxyphenylsuccinic acid, which in fact inhibited the succinic–maleic acid oxidation.

Brooke (*Annalen*, 1899, **305**, 21) observed that the solid obtained by the sudden cooling of molten benzylidenesuccinic acid contained a very small proportion of the isomeric maleic acid which at its melting point reverted almost completely to the itaconic acid. By the application of this thermal conversion process to *p*-methoxybenzylidenesuccinic acid (VI) there were obtained minute yields of the acid (VII), the ultra-violet absorption spectrum of which closely resembled that of citraconic acid and was readily distinguished from that of the parent acid. With the osmium tetroxide method the acid (VII) gave rise to one racemate of *p*-methoxybenzyltartaric acid (VIII; R = Me) which was resolved by means of its brucine salt, giving the (+)-isomeride identical with the *O*-methylpiscidic acid.

Experimental

Ethyl α-Acetoxy-γ-phenylacetoacetate.—Obtained (yield, *ca.* 60%) by the procedure employed by Attwood, Stevenson, and Thorpe (*J.*, 1923, **123**, 1755) for the preparation of the so-called ethyl "β-keto-γ-phenylbutyrate" (*i.e.*, ethyl γ-phenylacetoacetate), ethyl α-phenylacetoacetate was a pale yellow oil, b. p. 110°/0·8 mm., with a purple ferric reaction. The 2 : 4-*dinitrophenylhydrazone* separated from ethyl acetate in yellow needles, m. p. 94—95° (Found: N, 15·5. $C_{18}H_{18}O_6N_4$ requires N, 15·8%).

Lead tetra-acetate (22 g.) was added portion-wise to a stirred solution of this ester (10·2 g.) in acetic acid (25 ml.) at <40°. The mixture was diluted with water (50 ml.) and extracted with ether, giving *ethyl α-acetoxy-α-phenylacetoacetate* as a colourless oil (5 g.), b. p. 128—130°/0·2 mm. with a negative ferric reaction (Found: C, 63·8; H, 6·2. $C_{14}H_{16}O_5$ requires C, 63·6; H, 6·1%). The absence of a ferric reaction with this derivative served to confirm that the parent ester is ethyl α-phenylacetoacetate as suggested by Scheibler, Emden, and Krabbe (*Ber.*, 1930, **63**, 1562).

(*a*) Lead tetra-acetate (44·3 g.) was added portion-wise to a stirred solution of ethyl γ-phenylacetoacetate (Sonn and Litten, *Ber.*, 1933, **66**, 1512) in acetic acid (40 ml.) at <40° and the yellow viscous reaction mixture treated with water (120 ml.). The resulting *ethyl α-acetoxy-γ-phenylacetoacetate* was isolated with ether and on distillation was obtained as a bright yellow oil (10 g.), b. p. 143—145°/0·5 mm., which on being kept for several months became colourless; distillation of the colourless specimen regenerated the yellow oil (Found: C, 63·7; H, 6·3%). This compound had a deep cherry-red ferric reaction in alcohol.

(*b*) Phenylacetyl bromide (4 g.) was added dropwise to ethyl diazoacetate kept at −5° during ½ hr. and the resulting viscous product, which did not solidify, was heated with acetic acid (3 g.) on the steam-bath for 20 min. From the reaction mixture, which had been diluted with water (80 ml.), ethyl α-acetoxy-γ-phenylacetoacetate was isolated with ether and on distillation in a vacuum obtained as a yellow oil (0·8 g.) identical with the ester prepared by method (*a*).

Ethyl α-Benzyltartrate.—A mixture of ethyl α-acetoxy-γ-phenylacetoacetate (2·6 g.), hydrogen cyanide (0·6 ml.), and powdered sodium hydroxide (0·1 g.) was kept for 12 hr., diluted with alcohol (20 ml.), saturated with hydrogen chloride, heated under reflux for 4 hr., cooled, and filtered to remove ammonium chloride. Triturated with a little ether, the residue left on evaporation of the filtrate solidified and on crystallisation from methanol gave *ethyl benzyltartrate* as a mixture (0·4 g.) of needles and prisms which were separated manually and by repeated recrystallisation into approximately equal amounts of *racemate* (A) which formed needles, m. p. 174—175°, from

methanol (Found: C, 60·1; H, 6·8. $C_{15}H_{20}O_6$ requires C, 60·8; H, 6·8%) and *racemate* (B), irregular prisms, m. p. 194—195°, from acetic acid (Found: C, 60·2; H, 6·7%). With methanolic ammonia racemate (A) gave a *diamide* which separated from 90% alcohol in parallelopipeds, m. p. 204—206° (decomp.) (Found: N, 11·4. $C_{11}H_{14}O_4N_2$ requires N, 11·8%). Similarly racemate (B) gave a *diamide*, rectangular plates, m. p. 185—186° (decomp.), from alcohol (Found: N, 11·4%).

α-Hydroxy-β-phenylsuccinic Acid (*β-Phenylmalic Acid*).—Ethyl phenyloxaloacetate (Wislicenus, *Ber.*, 1894, **27**, 1091) (10 g.) was reduced by moist aluminium amalgam (from 8 g. of aluminium) in ether (200 ml.) with the addition of small amounts of water during 3—5 hr.; the completion of the reaction was indicated by the negative ferric reaction of a test portion. On distillation, the resulting *ethyl β-phenylmalate* was obtained as a colourless oil (8 g.), b. p. 131°/0·04 mm. (Found: C, 63·0; H, 7·0. $C_{14}H_{18}O_5$ requires C, 63·2; H, 6·8%). This ester (20 g.) was hydrolysed with 10% aqueous potassium hydroxide (120 ml.) and on being kept in a vacuum over phosphoric oxide the resulting syrupy acid crystallised, having m. p. 150—160°, after purification from ethyl acetate; the yield was 14 g. Fractional crystallisation of this from ethyl acetate and then ethyl acetate–light petroleum (b. p. 60—80°) gave the less soluble racemic *isomeride* (A), forming irregular prisms, m. p. 172°, from ethyl acetate (Found: C, 57·3; H, 4·7. $C_{10}H_{10}O_5$ requires C, 57·2; H, 4·8%), and the more soluble racemic *isomeride* (B) which separated from ethyl acetate–light petroleum in elongated hexagonal prisms, m. p. 162° (Found: C, 57·2; H, 4·6%).

A mixture (3 g.) of (A) and (B) was boiled with acetic anhydride (20 g.) for 3 hr., and about half of the anhydride distilled. On cooling, the residue deposited phenylmaleic anhydride in colourless rectangular plates (1·7 g.), m. p. 120°, which on treatment with alkali furnished phenylmaleic acid, m. p. 90—92° (decomp), quantitatively (cf. Alexander, *Annalen*, 1890, **258**, 67).

Phenyltartaric Acid.—On the addition of pyridine (2 ml.) a solution of phenylmaleic acid (1·54 g.) and osmium tetroxide (2 g.) in ether (200 ml.) became dark brown and slowly deposited a light brown precipitate. 2 Days later this osmium *adduct* (3·6 g.) was isolated with ether (Found: Os, 31·0. $C_{20}H_{18}O_4N_2Os$ requires Os, 31·5%), and treated with 7% aqueous potassium hydroxide (20 ml.). After the removal of the liberated pyridine with ether the red solution was acidified with hydrochloric acid, extracted twice with a little benzene, and evaporated over phosphoric oxide in a vacuum at room temperature. Extraction of the residue in a Soxhlet apparatus with ether gave *phenyltartaric acid*, which separated from ethyl acetate in hexagonal prisms (0·6 g.), m. p. 173—174°, soluble in water, alcohol, or acetone and insoluble in benzene or chloroform (Found: C, 53·0; H, 4·4. $C_{10}H_{10}O_6$ requires C, 53·1; H, 4·4%).

C-*Methyltartaric Acid.*—A mixture of citraconic acid (10 g.), sodium chlorate (12 g.), 1% aqueous osmium tetroxide (10 ml.), and water (150 ml.) was kept at 50° for 3 hr., cooled, extracted with benzene, basified with ammonia, and treated with a concentrated solution of barium acetate (30 g.) in water. The resulting barium salt was decomposed with a slight excess of dilute sulphuric acid, the excess of sulphuric acid was removed, and the filtered liquor concentrated in a vacuum, and finally dried over phosphoric oxide at room temperature, giving a solid which on recrystallisation from ethyl acetate furnished methyltartaric acid in colourless prisms (8 g.), m. p. 144—145° (Found: C, 36·4; H, 4·8; equiv., 84·1. Calc. for $C_5H_8O_6$: C, 36·6; H, 4·9%; equiv., 82·0) (cf. Schmidt and Perkow, *Chem. Ber.*, 1950, **83**, 484, who give m. p. 146°). This compound is easily soluble in water or alcohol, and insoluble in ether, benzene, or chloroform. The methyl ester separated from light petroleum (b. p. 60—80°) in elongated rectangular prisms, m. p. 99—100° (Found: C, 43·9; H, 6·3. Calc. for $C_7H_{12}O_6$: C, 43·8; H, 6·2%), and the diamide in hexagonal prisms, m. p. 152—153° (decomp.), from 90% alcohol (Found: N, 16·9. Calc. for $C_5H_{10}O_4N_2$: N, 17·3%) (cf. Schmidt and Perkow, *loc. cit.*).

β-Hydroxy-α-p-methoxybenzylsuccinic Acid (*p-Methoxybenzylmalic Acid*).—When the initial reaction between sodium ethoxide (prepared *in situ* from 7·2 g. of sodium and 18·16 ml. of alcohol) in ether (140 ml.) and ethyl oxalate had subsided, ethyl β-*p*-methoxyphenylpropionate (32 g.) was introduced and the mixture heated under reflux for 16 hr., poured on ice, and acidified. The product was isolated with much ether, and the ethereal solution was concentrated to *ca.* 200 ml. and repeatedly extracted with small amounts of 25% aqueous potassium carbonate until the residue left on evaporation of the ethereal solution gave a negative ferric reaction. The combined aqueous potassium carbonate extracts were acidified with dilute sulphuric acid and extracted with ether, and the combined extracts, containing ethyl α-ethoxalyl-β-*p*-methoxyphenylpropionate, were treated with an excess of moist aluminium amalgam (from 8 g. of aluminium). On isolation the resulting *ethyl β-hydroxy-α-p-methoxybenzylsuccinate* was obtained as

a colourless oil (28 g.), b. p. 75—77°/0·1 mm. (Found: C, 62·2; H, 7·3. $C_{16}H_{22}O_6$ requires C, 61·9; H, 7·1%). Hydrolysis of this ester (6 g.) with boiling 10% aqueous potassium hydroxide (35 ml.) gave the mixture of acids as a syrup which crystallised in contact with ethyl acetate–light petroleum (b. p. 60—80°), having m. p. *ca.* 130° (4·5 g.). Fractional crystallisation of this solid from the same solvent ultimately gave *racemate* (A) in colourless leaflets, m. p. 136—137° (Found: C, 56·8; H, 5·4. $C_{12}H_{14}O_6$ requires C, 56·7; H, 5·5%), and *racemate* (B) in rhombic prisms, m. p. 125—126° (Found: C, 56·9; H, 5·7%).

p-*Methoxybenzylidenesuccinic Acid.*—(*a*) A solution of the foregoing mixture of racemic acids (A) and (B) (2·3 g.) in acetic anhydride (15 ml.) was boiled for 3 hr. and concentrated in a vacuum to 5 ml. On cooling, this gave a quantitative yield of p-*methoxybenzylidenesuccinic anhydride* which separated from ethyl acetate in irregular prisms, m. p. 160° (Found: C, 66·1; H, 4·7. $C_{12}H_{10}O_4$ requires C, 66·1; H, 4·6%). This compound is insoluble in aqueous sodium hydrogen carbonate and readily decolorised aqueous potassium permanganate. On being boiled with water it gave *p*-methoxybenzylidenesuccinic acid, m. p. and mixed m. p. 194—195° (decomp.).

(*b*) A mixture of anisaldehyde (8·25 g.), ethyl succinate (10·5 g.), and alcoholic sodium ethoxide (from 7 g. of sodium and 70 ml. of alcohol) was boiled for 3 hr., the greater part of the alcohol was evaporated in a vacuum and replaced by an equal volume of water, and the solution concentrated to *ca.* 35 ml. Acidification with hydrochloric acid then gave p-*methoxybenzylidenesuccinic acid* which was purified by means of aqueous sodium carbonate and crystallised from acetic acid, forming colourless needles (8 g.), m. p. 194—195° (decomp.), readily soluble in alcohol or ethyl acetate and moderately soluble in chloroform, hot water, or benzene (Found: C, 61·3; H, 5·3%; equiv., 117·7. $C_{12}H_{12}O_5$ requires C, 61·0; H, 5·1%; equiv., 118). With boiling acetic anhydride this acid (10 g.) gave the anhydride (8·2 g.), m. p. 160°, which by the boiling methanol–sulphuric acid method (6 hr.) furnished *methyl* p-*methoxybenzylidenesuccinate* as a viscous oil, b. p. 165°/0·5 mm. (70%) (Found: C, 63·5; H, 7·8. $C_{14}H_{16}O_5$ requires C, 63·6; H, 7·6%).

p-*Methoxybenzylsuccinic Acid.*—(*a*) Hydrogenation of the foregoing benzylidenesuccinic acid (4·7 g.) in methanol (150 ml.) with hydrogen and a palladium catalyst (from 0·2 g. of palladium chloride and 1 g. of charcoal) gave p-*methoxybenzylsuccinic acid* as a viscous oil which crystallised from benzene in rosettes of needles (4 g.), m. p. 98—101° (Found: 60·3; H, 5·8. $C_{12}H_{14}O_5$ requires C, 60·5; H, 5·9%). By the same procedure methyl *p*-methoxybenzylidenesuccinate gave *methyl* p-*methoxybenzylsuccinate* as a colourless oil, b. p. 156°/1 mm., which slowly solidified, m. p. 35—37° (Found: C, 63·2; H, 6·7. $C_{14}H_{18}O_5$ requires C, 63·2; H, 6·8%). On hydrolysis this ester regenerated the acid, m. p. and mixed m. p. 98—101°. Distillation of *p*-methoxybenzylsuccinic acid (3·5 g.) at 180°/0·5 mm. gave the *anhydride* which separated from ethyl acetate–light petroleum (b. p. 60—80°) in needles (2·3 g.), m. p. 91—92°, readily soluble in acetone or benzene (Found: C, 65·3; H, 5·3. $C_{12}H_{12}O_4$ requires C, 65·5; H, 5·5%).

(*b*) *p*-Methoxybenzyl alcohol (1·9 g.) (Davidson and Bogert, *J. Amer. Chem. Soc.*, 1935, **57**, 905) was converted into *p*-methoxybenzyl chloride with phosphorus trichloride (2·5 g.) in ether (30 ml.); this was obtained as an unstable oil (5·2 g.), b. p. 125—127°/25 mm. Interaction of this chloride (20 g.) with ethyl sodiomalonate (from 20 g. of ester and 2·9 g. of sodium) in alcohol (60 ml.) at room temperature and then on the steam-bath for 4 hr. gave *ethyl* p-*methoxybenzylmalonate* (18 g.), b. p. 145°/0·5 mm. (Found: C, 64·5; H, 7·1. $C_{15}H_{20}O_5$ requires C, 64·3; H, 7·1%). A mixture of this ester (28 g.), sodium (2·3 g.), and alcohol (60 ml.) was heated under reflux for 2 hr., cooled, treated dropwise with ethyl bromoacetate (16·7 g.) during ½ hr., and then boiled for 2 hr. On isolation the resulting *ethyl α-ethoxycarbonyl-α-p-methoxybenzylsuccinate* was obtained as a colourless viscous liquid (23 g.), b. p. 166—169°/0·2 mm. (Found: 62·5; H, 7·3. $C_{19}H_{26}O_7$ requires C, 62·3; H, 7·1%). This succinate (12·3 g.) was heated with a solution of potassium hydroxide (14 g.) in 50% alcohol (75 ml.) on the steam-bath until a homogeneous solution was formed; this was then kept for 24 hr. and acidified. Isolated with ether, *α-carboxy-α-p-methoxybenzylsuccinic acid* was digested with hot benzene (80 ml.) and crystallised from ethyl acetate–light petroleum (b. p. 60—80°), forming elongated rectangular prisms (7·5 g.), m. p. 157—159° (decomp.) (Found: C, 55·4; H, 5·0. $C_{13}H_{14}O_7$ requires C, 55·3; H, 5·0%). When this was heated at 160°/25 mm. for 15 min. and the residue crystallised from hot water, this acid (2 g.) gave *p*-methoxybenzylsuccinic acid, m. p. and mixed m. p. 98—100°.

A stirred mixture of *N*-bromosuccinimide (3·6 g.), *p*-methoxybenzylsuccinic anhydride (2·2 g.), carbon tetrachloride (40 ml.), and benzoyl peroxide (0·02 g.) was heated under reflux for 12 hr.; the solution became red and after 1—2 hr. hydrogen bromide was evolved. The filtered mixture was evaporated and the reddish-brown residue extracted with ethyl acetate,

giving *p*-methoxybenzylidenesuccinic anhydride, m. p. and mixed m. p. 159—160°. The same product was formed with carbon disulphide as the solvent.

p-*Methoxybenzylmaleic Acid.*—*p*-Methoxybenzylidenesuccinic anhydride (45 g.) was heated in a Pyrex tube (oil-bath at 180°) until completely molten and then rapidly poured on to a cold sheet of glass. The solid was immediately pulverised and heated with carbon disulphide (100 ml.) under reflux for 20 min., collected, and washed with more solvent (100 ml.). After having been freed from traces of carbon disulphide the unchanged acid was remelted and the process repeated. Evaporation of the combined carbon disulphide extracts from 22 experiments (equivalent to 891 g. of the benzylidenesuccinic anhydride) left an orange semi-solid which was extracted with a little ether, leaving a trace of the benzylidenesuccinic anhydride. The residue left on evaporation of the ether was extracted with light petroleum (b. p. 40—60°) and, on cooling, the solution deposited p-*methoxybenzylmaleic anhydride*, m. p. 64—65°, which, on recrystallisation from chloroform–light petroleum (b. p. 60—80°), formed almost colourless prisms, m. p. 65—66° (yield 1·85 g. from 22 experiments) (Found: C, 66·2; H, 4·7. $C_{12}H_{10}O_4$ requires C, 66·1; H, 4·6%). This compound is readily soluble in alcohol, benzene, or chloroform. On being melted, it reverts almost completely to *p*-methoxybenzylidenesuccinic anhydride, m. p. 160°.

p-Methoxybenzylmaleic anhydride (0·5 g.) was heated with water (30 ml.) (shake) at 55—60° for 2 hr. and the solution filtered to remove a trace of solid and evaporated in a vacuum. The residue was washed with a little chloroform to recover unchanged anhydride and recrystallised from ethyl acetate–light petroleum (b. p. 60—80°), giving p-*methoxybenzylmaleic acid* in colourless rhombic plates (0·4 g.), m. p. 120° with sintering at 117°, readily soluble in alcohol, benzene, or acetone (Found: C, 61·2; H, 5·2. $C_{12}H_{12}O_5$ requires C, 61·0; H, 5·1%).

p-*Methoxybenzyltartaric Acid.*—Pyridine (0·5 ml.) and osmium tetroxide (0·5 g.) were added to a solution of *p*-methoxybenzylmaleic acid (0·47 g.) in ether (10 ml.), and the mixture kept in a closed vessel for 3 days. The light brown precipitate (1·2 g.) was collected, washed with ether, and treated with 7% aqueous potassium hydroxide (10 ml.), forming a deep purple solution. This was extracted with ether to remove pyridine, acidified, and evaporated in a vacuum at room temperature. The residue was extracted with ether in a Soxhlet apparatus for 9 hr. and the extract evaporated, leaving p-*methoxybenzyltartaric acid*, which separated from ethyl acetate in colourless prisms (0·2 g.), m. p. 205—207° (decomp.) (Found: C, 53·1; H, 5·1. $C_{12}H_{14}O_7$ requires C, 53·3; H, 5·2%).

Brucine (197 mg.) was added to a hot solution of *p*-methoxybenzyltartaric acid (67·5 mg.) in water (5 ml.), and the mixture decanted from a trace of solid and concentrated in a vacuum over phosphoric oxide at room temperature to *ca.* 3 ml. The brucine salt, which had separated in rectangular prisms (48 mg.), was collected, washed with a little water, and dried; it had $[\alpha]_D^{23\cdot5}$ −14·39° ± 0·6° (*c*, 2·96 in 50% alcohol). This salt (40 mg.) was decomposed with 10% aqueous sodium carbonate, the solution was filtered to remove the precipitate of brucine (wash with water), the filtrate and washing were evaporated in a vacuum at room temperature, and the residue was continuously extracted with chloroform to remove traces of brucine. The solid was then decomposed with hydrochloric acid, the mixture evaporated in a vacuum at room temperature, and the residue extracted with ether, giving *p-O*-methylpiscidic acid, $[\alpha]_D^{23}$ +44·01° ± 5·0° (*c*, 1·262 in H_2O), m. p. 169—170°, undepressed on admixture with a natural specimen. Mixed with the racemic acid, m. p. 205—207°, it melted at 173—176°.

Derivatives of Piscidic Acid.—The monomethyl ester had $[\alpha]_D^{23}$ +41·52° (*c*, 1·325 in H_2O), the monoethyl ester $[\alpha]_D^{17\cdot5}$ +59·70° (*c*, 1·551 in EtOH), the dimethyl ester $[\alpha]_D^{19}$ +23·71° (*c*, 6·367 in EtOH), methyl *p-O*-methylpiscidate $[\alpha]_D^{18°}$ +78·16° (*c*, 1·54 in EtOH), and methyl *p-O*-benzylpiscidate $[\alpha]_D^{19}$ +48·73° (*c*, 1·786 in EtOH) (Part I, *loc. cit.*).

Hydrolysis of methyl *p-O*-methylpiscidate (1 g.) with 10% aqueous potassium hydroxide (10 ml.) on the steam-bath for 5 hr. gave p-O-*methylpiscidic acid* which separated from ethyl acetate–light petroleum (b. p. 60—80°) in elongated rectangular prisms, m. p. 169—170, $[\alpha]_D^{22\cdot5}$ +41·97° (*c*, 1·129 in H_2O) (Found: C, 53·4; H, 5·2%; equiv., 136·7. $C_{12}H_{14}O_7$ requires C, 53·3; H, 5·2%; equiv., 135). Cinchonine (294 mg.) was added to a hot solution of this acid (135 mg.) in alcohol (3 ml.), and the solution decanted from a little solid and diluted with water (7 ml.). The *cinchonine* salt was collected several days later and recrystallised from dilute alcohol, forming rectangular prisms, $[\alpha]_D^{17}$ +139·6° (*c*, 6·1 in EtOH) (Found: N, 6·8. $C_{50}H_{58}O_9N_4$ requires N, 6·5%). Similarly prepared, the *brucine* salt separated from hot water in rectangular prisms, $[\alpha]_D^{24}$ −13·03° (*c*, 2·131 in 50% alcohol) (Found: N, 5·4. $C_{58}H_{66}O_{15}N_4$ requires N, 5·3%).

Cinchonine piscidate separated from dilute alcohol in clusters of needles, $[\alpha]_D^{21}$ +146·2° (*c*,

0·424 in EtOH) [Found: N, 6·9. $C_{11}H_{12}O_7,(C_{19}H_{22}N_2O)_2$ requires N, 6·6%], and the (+)-N-*methylphenylisopropylamine* salt in elongated hexagonal prisms, m. p. 179°, $[\alpha]_D^{24}$ +12·73° (*c*, 2·09 in H_2O) (Found: N, 3·7. $C_{11}H_{12}O_7,C_{10}H_{15}N$ requires N, 3·8%).

p-*Methoxyphenyl-lactic Acid.*—Reduction of *p*-methoxyphenylpyruvic acid (5 g.) in 5% aqueous sodium hydroxide (50 ml.) with 2% sodium amalgam (150 g.) gave p-*methoxyphenyl-lactic acid*, forming elongated rectangular prisms (3·5 g.), m. p. 88°, from ethyl acetate–light petroleum (b. p. 60—80°), soluble in alcohol or acetone and insoluble in chloroform or benzene (Found: C, 61·0; H, 6·3. $C_{10}H_{12}O_4$ requires C, 61·22; H, 6·1%). Prepared by hot methanolic sulphuric acid, the *methyl* ester was a colourless oil, b. p. 135°/0·1 mm. (Found: C, 62·7; H, 6·8. $C_{11}H_{14}O_4$ requires C, 62·9; H, 6·7%).

Methylation of this methyl ester (3·9 g.) with silver oxide (8 g.) in an excess of boiling methyl iodide for 7 hr. gave the *methyl ether* of methyl *p*-methoxyphenyl-lactate as a colourless oil (3·7 g.), b. p. 120°/0·5 mm. [Found: OMe, 40·7. $C_9H_7O(OMe)_3$ requires OMe, 41·5%]. This compound did not appear to condense readily and attempts to synthesise an *O*-dimethyl ether of piscidic acid by way of the oxalo-derivative were abandoned.

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Interaction of Polynitro-compounds with Aromatic Hydrocarbons and Bases. Part XIII. The Effect of changing the Nitro-compound.*

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The results are recorded of a study of the interactions in *cyclo*hexane solution of a number of *N*-alkylanilines with a series of nitrobenzenes. Association constants as defined in Part XII * have been taken as a measure of the degree of interaction of the two components and are discussed in the light of charge-transfer (Mulliken, *J. Amer. Chem. Soc.*, 1952, **74**, 811; *J. Phys. Chem.*, 1952, **56**, 801).

THE interactions of a number of nitrobenzenes have been studied with a view to displaying the effect of the number and orientation of the nitro-groups on the association constants. Increase in the number of nitro-groups is expected to augment the Lewis acidity of nitrobenzene. Introduction of methyl groups (*e.g.*, *s*-trinitrotoluene) may be expected (apart from possible steric effects) to diminish the Lewis acidity. The bases used for the interactions with the nitro-compounds were chosen to reveal whether or not the order of apparent Lewis acidities of the nitro-compounds is independent of the base.

EXPERIMENTAL

The association constants for the interactions were determined by the colorimetric method previously described (Foster, Hammick, and Wardley, *J.*, 1953, 3817). Optical densities were measured in 10-mm. cells. A Beckman Quartz Spectrophotometer (model DU) was used.

All the determinations were made in *cyclo*hexane. The results quoted in the Table represent the mean of two or more determinations. The individual results in all cases are within ±0·15 l./mole of the mean values quoted. Owing to absorption by the components, none of the solutions had a spectrum showing a maximum characteristic of the complex. However, it has been shown (Foster and Hammick, *J.*, 1954, 2685) that, for example, in the case of the *NN*-dimethylaniline–*s*-trinitrobenzene interaction, the photometric estimation of the concentration of a complex at wave-lengths other than its characteristic maximum is possible, provided that the wave-length used is away from the absorption bands of either component. For these reasons, most of the estimations were made in the region 450—480 mμ. No attempt has been made to resolve the spectra of the complexes from the spectra of the components at shorter wave-lengths and so to find the wave-length of maximum absorption due to the complex.

Materials.—Aniline, *N*-alkylanilines, and *cyclo*hexane were purified as described by Foster and Hammick (*loc. cit.*). Nitrobenzene (I), prepared by the nitration of pure benzene, had

* Part XII, *J.*, 1954, 2685.

b. p. 210°/761 mm. *o*-Dinitrobenzene (II), recrystallised four times from aqueous alcohol, had m. p. 118°.

m-Dinitrobenzene (III), recrystallised three times from aqueous alcohol, had m. p. 88°. *p*-Dinitrobenzene (IV) recrystallised four times from aqueous alcohol, had m. p. 172°.

Association constants of nitrobenzene–alkylaniline complexes * *in* cyclo*hexane at* 18·5—20°.

Aniline derivative	(I)	(II)	(III)	(IV)	(V)	(VI)	(VII)	(VIII)	pK_a [d]
(Aniline)	—[a]	—[a]	—[a]	0·5	3·1 [b]	2·7	—[c]	—[a]	4·58
N-Methyl-	0·3	0·5	0·4	0·9	7·3 [b]	3·1 [b]	1·7	—[a]	4·85
N-Ethyl-	0·3	0·8	0·7	1·2	8·4 [b]	3·8 [b]	2·0	—[a]	5·11
NN-Dimethyl-	0·4	1·1	1·2	1·8	9·5 [b]	5·8 [b]	—[c]	—[a]	5·06
NN-Diethyl-	0·3	1·1	1·4	1·7	6·5 [b]	2·4 [b]	—[c]	—[a]	6·56

* For numerals in column headings, see nitro-derivatives recorded in the text; (V) is trinitrobenzene.

[a] Too small to measure. [b] Foster and Hammick (*loc. cit.*). [c] Not measurable owing to the low solubility of *s*-trinitro-*m*-xylene in the respective alkylanilines. [d] From Hall and Sprinkle (*J. Amer. Chem. Soc.*, 1932, **54**, 3469).

s-Trinitrotoluene (VI), recrystallised twice from alcohol, had m. p. 81°. *s*-Trinitro-*m*-xylene (VII) prepared by Beilstein and Luhmann's method (*Annalen*, 1867, **144**, 274), had m. p. 182°. Trinitromesitylene (VIII), recrystallised twice from alcohol, had m. p. 232°.

Discussion

It is assumed that these interactions may be described as charge-transfer processes (Mulliken, *J. Amer. Chem. Soc.*, 1952, **74**, 811; *J. Phys. Chem.*, 1952, **56**, 801; Foster and Hammick, *loc. cit.*). The Lewis acids are the nitro-compounds, the Lewis bases are the anilines.

The order of the stabilities of the complexes of *s*-trinitrobenzene with certain alkylanilines has already been shown to be: aniline < *N*-methyl- < *N*-ethyl- < *NN*-dimethyl- > *NN*-diethyl-aniline (Foster and Hammick, *loc. cit.*). This also appears to be the order of stability of the complexes of these alkylanilines with *o*-, *m*-, and *p*-dinitrobenzene. A possible exception is the *m*-dinitrobenzene–*NN*-dimethylaniline complex, which may be less stable than the *NN*-diethylaniline complex; in this case, however, it will be seen that the difference is within the experimental error. In the case of the mononitrobenzene complexes the experimental error is too large to permit the assignment of an order to the complex stabilities, except that *NN*-dimethylaniline has the highest and aniline the lowest association constant.

This order is not the order of the Brønsted basicities of the respective alkylanilines (last column in the Table). The pK_a values are a measure of the relative stability of the anilinium ion in which a proton has been added to the nitrogen atom of the aniline molecule. In the case of the association constants a measure is being made of the Lewis basicities of the π-orbital of the respective anilines. This orbital, though it extends over the nitrogen atom, is not localised on it. Also the Lewis acid which it attracts, namely, the nitrobenzene molecule, is of a shape which will involve stereochemical factors absent in the case of the proton–aniline interaction.

The order of the degrees of interaction of a given aniline with the various nitrobenzenes appears to be: nitrobenzene < *o*-dinitrobenzene = *m*-dinitrobenzene < *p*-dinitrobenzene < *s*-trinitrobenzene > *s*-trinitrotoluene > *s*-trinitro *m*-xylene > trinitromesitylene. In the case of the dinitrobenzenes the results suggest that the *p*-isomer may have the lowest electron density in the π-orbital. The various dinitrobenzene isomers may also differ in their steric interference with the approach of an aniline molecule. *s*-Trinitrobenzene with three nitro-groups symmetrically disposed about the benzene ring behaves as a much stronger Lewis acid.

The introduction of methyl groups successively into the remaining unsubstituted positions in *s*-trinitrobenzene causes a rapid fall in the stability of the complexes. This may be due to a combination of two effects. The methyl groups will by their inductive effect tend to increase the electron density of the π-orbital, thus decreasing the potential Lewis acidity (Hammick and Hellicar, *J.*, 1938, 761). Also the introduction of a methyl group *ortho* to nitro-groups will cause some steric interference. In particular the nitro-

groups may no longer be able to lie in the plane of the benzene ring. In the case of *s*-trinitrotoluene, a planar configuration may be obtained with only a small adjustment of the bond angles. However, in *s*-trinitro-*m*-xylene and trinitromesitylene one or more groups are effectively held out of the plane of the ring. The result is a loss of resonance of the nitro-groups with the benzene ring so that the electromeric removal of electrons by the nitro-groups is hindered. Thus again the Lewis acidity is reduced. Other evidence for the steric inhibition of resonance of this type has been given by Brown and Reagan (*J. Amer. Chem. Soc.*, 1947, **69**, 1032) and by Fielding and Le Fèvre (*J.*, 1950, 2812).

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Nuclear Oxidation of Flavones and Related Compounds. Synthesis of Gardenin.

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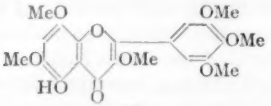
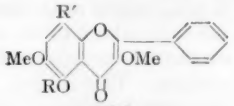
Gardenin has been synthesised from myricetin 3 : 3′ : 4′ : 5′-tetramethyl ether. The important stages are (1) nuclear reduction of the 7-position, (2) *para*-nuclear oxidation of the 8-position with alkaline persulphate, and (3) *ortho*-nuclear oxidation of the 6-position.

GARDENIN (I), the yellow crystalline component of Dikamali gum (gum of *Gardenia lucida*), was isolated by Stenhouse and Groves (*J.*, 1877, 552; *Annalen*, 1880, **200**, 311). Its constitution has been established as 5-hydroxy-3 : 6 : 8 : 3′ : 4′ : 5′-hexamethoxyflavone (I) (Bose and Nath, *J. Indian Chem. Soc.*, 1938, **15**, 138; Bose, *ibid.*, 1945, **22**, 233; Balkrishna and Seshadri, *Proc. Indian Acad. Sci.*, 1948, **27**, *A*, 91, 260). It thus belongs to an unusual type of flavonol derivatives and is the only representative known. In the scheme of biogenesis (Balkrishna and Seshadri, *loc. cit.*) it was derived from the fundamental group of 5 : 7-dihydroxyflavonols by processes involving nuclear reduction of the 7-position and nuclear oxidation of the 6- and the 8-position. Illustrating one possible route, the synthesis of the lowest member of the series, 3 : 5 : 6 : 8-tetramethoxyflavone (II*a*) (Balkrishna and Seshadri, *loc. cit.*), involved 5-hydroxy-3 : 6-dimethoxyflavone (II*b*), its *para*-nuclear oxidation with alkaline persulphate (to II*c*), and methylation.



(I)



(II)

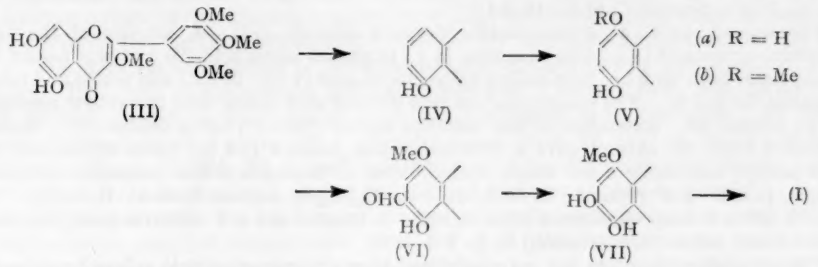
(*a*) R = Me, R′ = OMe

(*b*) R = R′ = H

(*c*) R = H, R′ = OH

Gardenin (I) itself has now been synthesised by an alternative route which involves *ortho*-oxidation of the appropriate 5 : 8-dihydroxyflavone (V*a*) in the 6-position, followed by methylation. Myricetin 3 : 3′ : 4′ : 5′-tetramethyl ether (III) which is readily obtained by Allan–Robinson synthesis (Kalff and Robinson, *J.*, 1925, 181) is the convenient starting point and is subjected to toluene-*p*-sulphonylation in the 7-position and hydrogenolysis with Raney nickel [Ramanathan and Venkataraman, *Proc. Indian Acad. Sci.*, 1953, **38**, *A*, 40; 1954, **39**, *A*, 90; Jain and Seshadri, *J. Sci. Ind. Res.* (*India*), 1953, **12**, *B*, 503; 1954, **13**, *B*, 310]. This method of preparation of 5-hydroxyflavonols is more convenient than the older method employing γ-resacetophenone (Seshadri, Varadarajan, and Venkateswarlu, *Proc. Indian Acad. Sci.*, 1950, **32**, *A*, 250). The present method of nuclear reduction is also in accordance with the scheme of biogenesis. The resulting 5-hydroxy-compound (IV) undergoes persulphate oxidation satisfactorily, to yield the quinol (V*a*) which is a tetramethyl ether of the highest member of the 3-hydroxyprimetin series; the lower members were prepared earlier by nuclear oxidation (Seshadri, Varadarajan, and Venkateswarlu, *loc. cit.*; Ramanathan and Venkataraman, *ibid.*,

1954, **39**, *A*, 90). The quinol (V*a*) is partially methylated and the product (V*b*), which gives all the reactions of a compound containing a free 5-hydroxy-group, is subjected to aldehyde synthesis with hexamine. The yield of the aldehyde (VI) is low (20%) owing to formation of a by-product. The subsequent Dakin oxidation gives a good yield (60%)



of the catechol derivative (VII). A final partial methylation yields gardenin (I) identical with an authentic sample obtained from Dikamali gum.

Experimental

5-Hydroxy-3 : 3′ : 4′ : 5′-tetramethoxy-7-toluene-p-sulphonyloxyflavone.—A suspension of 5 : 7-dihydroxy-3 : 3′ : 4′ : 5′-tetramethoxyflavone (III) (6 g.) in acetone (400 c.c.) containing toluene-*p*-sulphonyl chloride (3·3 g.) and potassium carbonate (8 g.) was refluxed for 4 hr. Acetone was then distilled off, water (300 c.c.) added to the residue, and the solution acidified with dilute hydrochloric acid. The yellow solid was collected, washed with water, and crystallised from acetone, yielding lemon-yellow needles and narrow rectangular plates (6·6 g.) of the *toluene-p-sulphonate*, m. p. 172—173° (Found, in a sample dried at 120°: C, 59·1; H, 4·7. $C_{26}H_{24}O_{10}S$ requires C, 59·1; H, 4·5%). It gives a brown colour with ferric chloride and a sparingly soluble yellow sodium salt with aqueous sodium hydroxide.

5-Hydroxy-3 : 3′ : 4′ : 5′-tetramethoxyflavone (IV).—The above ester (4 g.) in alcohol (500 c.c.) and Raney nickel (12 g.) were stirred in hydrogen at 40° for 1·5 hr. The mixture was filtered and the nickel washed twice with hot alcohol. The filtrate was concentrated to 100 c.c. and treated with potassium hydroxide (3 g.) in a small amount of water, and the solution refluxed for 1 hr. Alcohol was then removed under reduced pressure, and the residue taken up in water and acidified. The precipitate (2 g.) was extracted with cold benzene (3 × 50 c.c.) (undissolved solid S), benzene was distilled off, and the residue crystallised from ethanol, yielding golden-yellow rectangular plates and prisms (0·7 g.), m. p. 131—132°, of the *5-hydroxyflavone* (Found: C, 63·9; H, 5·4. $C_{19}H_{18}O_7$ requires C, 63·7; H, 5·0%). It gave a green ferric reaction and a sparingly soluble yellow sodium salt. The *acetate* crystallised from ethanol as colourless needles, m. p. 179—180° (Found: C, 62·5; H, 5·4. $C_{21}H_{20}O_8$ requires C, 63·0; H, 5·0%).

The undissolved solid (S) (1·2 g.), after crystallisation from pyridine, was identified as the original myricetin tetramethyl ether (III).

5 : 8-Dihydroxy-3 : 3′ : 4′ : 5′-tetramethoxyflavone (V*a*).—A stirred solution of the above 5-hydroxyflavone (3 g.) in pyridine (75 c.c.) and aqueous potassium hydroxide (5 g. in 125 c.c. of water), at 15—20°, was treated dropwise with potassium persulphate (5 g.) in water (250 c.c.) during 3 hr. After 24 hr. at room temperature the deep brown solution was acidified to Congo-red and the unchanged 5-hydroxy-compound (0·6 g.) filtered off, ether-extraction removing the last traces of it. The clear brown aqueous solution was heated with sodium sulphite (4 g.) and concentrated hydrochloric acid (100 c.c.) at 100° for 0·5 hr. It was then cooled and the yellow solid was filtered off and washed with water. The filtrate on ether extraction gave some more of the *quinol*. This crystallised from dilute methanol as orange-yellow rectangular tablets, m. p. 179—180° (1·2 g.) (Found: C, 57·8; H, 5·3; loss at 110°, 4·8. $C_{19}H_{18}O_8,H_2O$ requires C, 58·2; H, 5·1; loss 4·6%. Found, in dried sample: C, 60·7; H, 5·2. $C_{19}H_{18}O_8$ requires C, 61·0; H, 4·8%). The ferric reaction was green, changing to brown.

The *diacetate* crystallised from benzene–light petroleum as colourless rectangular prisms, m. p. 178—179° (Found: C, 60·2; H, 5·3. $C_{23}H_{22}O_{10}$ requires C, 60·3; H, 4·8%).

5-Hydroxy-3 : 8 : 3′ : 4′ : 5′-pentamethoxyflavone (V*b*).—The quinol (2 g.), methyl iodide (2 c.c.), and ignited potassium carbonate (6 g.) in acetone (100 c.c.) were refluxed for 2 hr., then

filtered. Acetone was distilled off and the residue treated with water. The solid product crystallised from ethanol as golden-yellow prismatic needles and rods (1·9 g.), m. p. 147—148°, giving a stable green ferric reaction in ethanol (Found: C, 61·8; H, 4·9. $C_{20}H_{20}O_8$ requires C, 61·9; H, 5·1%).

The *acetate* formed colourless needles (from ethanol), m. p. 178—180° (Found: C, 61·2; H, 5·2. $C_{22}H_{22}O_9$ requires C, 61·4; H, 5·1%).

5-Hydroxy-3 : 8 : 3′ : 4′ : 5′-pentamethoxyflavone-6-aldehyde (VI).—A solution of the above 5-hydroxy-compound (1 g.) and hexamine (3 g.) in glacial acetic acid (20 c.c.) was heated on a boiling-water bath for 6 hr., then boiling hydrochloric acid (1 : 1; 20 c.c.) was added and heating continued for 0·5 hr. The cooled mixture was diluted with water, and the yellow precipitate (0·6 g.) filtered off. Extraction of this with hot alcohol (150 c.c.) left a residue (A). Removal of alcohol from the extract gave a brownish-yellow product (0·2 g.) which crystallised from ethyl acetate containing a few drops of chloroform as brownish-yellow prismatic needles and rods, m. p. 212—214° (Found: C, 60·5; H, 5·0. $C_{21}H_{20}O_9$ requires C, 60·6; H, 4·8%). This *aldehyde* gives a deep olive-green ferric reaction in ethanol and a 2 : 4-dinitrophenylhydrazone as brown-red plates (from ethanol), m. p. 268—270°.

The insoluble portion (A) (0·4 g.) crystallised from chloroform as pale yellow hairy needles, m. p. 277—279°, and did not give any ferric reaction or 2 : 4-dinitrophenylhydrazone.

5 : 6-Dihydroxy-3 : 8 : 3′ : 4′ : 5′-pentamethoxyflavone (VII).—A cooled (20°) solution of the above flavone-aldehyde (80 mg.) in pyridine (4 c.c.), 0·5N-sodium hydroxide (0·6 c.c.), and water (3 c.c.) was treated dropwise with hydrogen peroxide (0·3 c.c.; 6%) during 15 min. The solution, initially deep brownish-red, became pale yellow. After 2 hr. the mixture was acidified with ice-cold dilute hydrochloric acid, and the yellow precipitate was filtered off. The *dihydroxyflavone* crystallised from chloroform–methanol as deep yellow prisms (55 mg.), m. p. 200—202° (Found: C, 59·8; H, 5·3. $C_{20}H_{20}O_9$ requires C, 59·4; H, 5·0%). Its ferric reaction was brown, deepening with excess of reagent.

Gardenin (I).—The flavone (VII) (40 mg.) was refluxed with excess of methyl iodide and potassium carbonate in acetone for 1·5 hr. The product was crystallised from ether–light petroleum and finally from dilute alcohol and was obtained as golden-yellow needles, m. p. and mixed m. p. 163—165°. The colour reactions with ferric chloride and nitric acid (*d* 1·2) were identical with those for authentic gardenin.

UNIVERSITY OF DELHI, DELHI-8. [*Received, June 9th*, 1954.]

The Kinetics and Mechanisms of Addition to Olefinic Substances. Part II. Addition of Chlorine to Allyl Alcohol. The Intermediates involved in Electrophilic Addition Reactions.*

By P. B. D. DE LA MARE and J. G. PRITCHARD.

[Reprint Order No. 5504.]

The addition of chlorine to allyl alcohol in aqueous solution in the presence of chloride ions gives 2 : 3-dichloropropan-1-ol. Thus the hydroxyl substituent does not migrate to the 2-position in the course of the addition. The significance of this is considered in relation to the facts and theories concerning addition reactions.

IN the preceding paper, evidence was presented that when hypochlorous acid is added to allyl chloride some of the chlorine substituent already present in the molecule migrates to the 2-position in the product. The chlorine substituent is one of the least effective of those groups which, when β to a carbonium ionic centre, have the effect (Lucas and Gould, *J. Amer. Chem. Soc.*, 1941, **63**, 2541) of preserving the optical configuration at that centre by the formation of a bridged intermediate; at least, this is certainly so if participation of a substituent in this way is judged by the ability of the group to facilitate heterolysis (cf. Winstein, *Bull. Soc. chim.*, 1951, C 55; Winstein and Buckles, *J. Amer. Chem. Soc.*, 1942, **64**, 2787; Winstein and Grunwald, *ibid.*, 1948, **70**, 828). It is of interest to consider the effect of other, more effective participating groups when they are similarly situated. Of

* Part I, *J.*, 1954, 3910.

these, the hydroxyl group is one such, and so the addition of chlorine to allyl alcohol has a special interest.

General considerations suggest that the CH_2·OH group should release electrons rather more readily than does the CH_2Cl group, since the inductive electron-withdrawal by the chlorine substituent should be greater than that by the hydroxyl group. This is borne out by comparison of the relative reactivities of allyl alcohol and allyl chloride in electrophilic additions (Bythell and Robertson, *J.*, 1938, 179; Swedlund and Robertson, *J.*, 1945, 131). The data on orientation of addition to allyl alcohol are in agreement with this opinion. Hydrogen chloride gives 2-chloropropan-1-ol (Dewael, *Bull. Soc. chim. Belg.*, 1924, **33**, 504) though no quantitative study has been made of this reaction. By kinetic analysis, Lennart Smith *et al.* (Smith, *Z. physikal. Chem.*, 1918, **92**, 717; cf. Smith and Skyle, *Acta Chem. Scand.*, 1950, **4**, 39) showed that addition of hypochlorous acid to allyl alcohol gives 73% of 3-chloropropane-1 : 2-diol and 27% of 2-chloropropane-1 : 3-diol.*

In the present work, the addition of chlorine water to allyl alcohol has been studied. At high dilution and low temperature (cf. U.S.P. 2,711,023), the reaction gives mainly monochlorohydrins in the isomeric ratio indicated above, but in the presence of excess of chloride ions the reaction can be considerably diverted towards the formation of some dichlorohydrin. Kinetic analysis of the ether-extractable product shows that the latter is almost entirely 2 : 3-dichloropropan-1-ol. Thus no migration of the hydroxyl substituent to the central carbon atom has been detected.

Note Added in Proof.—Winstein and Goodman (*J. Amer. Chem. Soc.*, 1954, **76**, 4638) have recently provided evidence, generally in concordance with our findings, that the hydroxyl substituent does not migrate during the addition of ClOMe or BrOMe to allyl alcohol.

Experimental

A slight excess of chlorine was passed into a solution of allyl alcohol (25 ml.) in saturated aqueous sodium chloride (2 l.). The product was extracted with ether, and the extract was washed with sodium hydrogen sulphite solution and with water, dried, and fractionated. After removal of the ether, the following fractions were collected: (*a*) 2·1 g., b. p. 69—70°/9 mm., n_D^{25} 1·4823; (*b*) 4·3 g., b. p. 69°/9 mm., n_D^{25} 1·4820; (*c*) 6·8 g., b. p. 69°/9° mm., n_D^{25} 1·4820. The residue from column and still-pot gave on distillation 1 g., b. p. 180—190°, n_D^{25} 1·4820, and 2 g. of partly decomposed material of high b. p. Fractions (*b*) and (*c*) were bulked (20% yield) and subjected to kinetic analysis as follows. The dichlorohydrin (0·792 g.) was added at 0° to 0·0491N-sodium hydroxide (125 ml.), and at intervals samples (10 ml.) were pipetted into 0·0656N-hydrochloric acid (10 ml.) and back-titrated with 0·0491N-sodium hydroxide. The results were:

Time	0·00	69·7	101·9	150·7	209·3	271·1	305·6	∞
Titre (ml. of 0·0491N-NaOH)	3·32	3·66	3·83	4·05	4·24	4·52	4·67	13·36
10^2k_2 (l. mole^{-1} min.$^{-1}$)	—	1·02	1·06	1·05	1·03	1·01	1·03	—

The constancy of the rate coefficients, which agree with the value (10^2k_1 = 1·00 l. mole^{-1} min.$^{-1}$) recorded by de la Mare and Pritchard (*J.*, 1954, 1644) for 2 : 3-dichloropropan-1-ol, indicates the quantity of the isomeric dichlorohydrin, if present, to be less than 1%.

Discussion

Since intermediates with three-membered rings, *e.g.*, as annexed, are customarily held to be concerned in addition reactions, it is necessary to consider comparatively the orientation of ring opening with that observed in addition processes. The following Tables summarise some of the available data.

The mechanisms involved in ring-opening of ethylene oxides have been much discussed, for example, by Ingold ("Structure and Mechanism in Organic Chemistry," G. Bell and

* The literature contains some misconceptions on this and related points. Israel, Martin, and Soper (*J.*, 1950, 1282) seem to have misread Smith's early work, which they quote as evidence that 2-chloropropane-1 : 3-diol is the major product; their theoretical account therefore requires reconsideration. Read and Hurst (*J.*, 1922, **121**, 996) state without conclusive evidence that, from the reaction of chlorine water and allyl alcohol, 2-chloropropane-1 : 3-diol is formed, no mention being made of the isomer; this clearly also needs revision in the light of Smith's findings.

Sons, London, 1953). It seems generally agreed that anion-catalysed ring openings involve nucleophilic attack on the oxide molecule, with, correspondingly, the expected orientation of attack at the primary position. The HCl-catalysed ring openings generally have the kinetic form $v \propto [\text{oxide}][H^+][Cl^-]$; on the whole, they preserve orientation involving nucleophilic attack at the primary carbon atom, and they are therefore considered to involve to

(a) *Percentage of nucleophilic attack on the central carbon atom in addition to* $CH_2{:}CH{\cdot}CH_2X$.

Compound	$CH_2{:}CH{\cdot}CH_3$	$CH_2{:}CH{\cdot}CH_2{\cdot}OH$	$CH_2{:}CH{\cdot}CH_2Cl$
Reagent: HCl	100 [a]	*ca.* 100 [b]	100 [a]
Reagent: ClOH	91 [c]	73 [c]	30 [c,d]
Reagent: ICl	70 [e]	—	—

(b) *Percentage of nucleophilic attack on the central carbon atom in ring opening of substituted ethylene oxides.*

Compound	$CH_2{-}CH{\cdot}CH_3$ (O)	$CH_2{\cdot}CH{\cdot}CH_2{\cdot}OH$ (O)	$CH_2{\cdot}CH{\cdot}CH_2Cl$ (O)
Reagent: OR^-	2 [f]	0	0 [g]
Reagent: HCl	25 [c]	10 [c]	0 [c]
Reagent: $ROH{-}H_2SO_4$	50 [f]	22 [h]	*ca.* 2 [i]

[a] Kharasch, Kleiger, and Mayo, *J. Org. Chem.*, 1939, **4**, 430, 433; Kharasch, Norton, and Mayo (*ibid.*, p. 83) record that hydrogen iodide adds to allyl chloride giving exclusively 1-chloro-2-iodopropane. Our results (Part I, *loc. cit.*) suggest, however, that some interaction between the substituent halogen and the developing carbonium ionic centre might occur and divert nucleophilic attack to the 1-position occupied by the neighbouring substituent. One might predict on this basis that a small proportion of 2-chloro-1-iodopropane might be formed, though this might well have escaped detection. [b] Dewael, *Bull. Soc. chim. Belg.*, 1924, **33**, 504. [c] L. Smith and Skyle, *Acta Chem. Scand.*, 1950, **4**, 39, and papers there cited. [d] Part I, *J.*, 1954, . [e] Ingold and H. G. Smith, *J.*, 1931, 2742. [f] Chitwood and Freure, *J. Amer. Chem. Soc.*, 1946, **68**, 680. [g] Boyde and Marle, *J.*, 1908, 839. [h] Ingham and Nichols, *J. Amer. Chem. Soc.*, 1954, **76**, 4472. [i] Winstein and Goodman, *ibid.*, p. 4368.

a predominant extent nucleophilic attack on the oxonium cation (*A*). The proportion of the other isomeric product formed under acid conditions is thought to indicate partial reaction through the "open" "classical" carbonium cation; ring opening in this direction is facilitated by increasing electron release from the CH_2X group, as is exemplified in the horizontal comparisons of Table (b).

In the addition reactions, as compared with the oxide ring openings, there is always formed a much greater proportion of the isomer derived by nucleophilic attack at the central (secondary) carbon atom. The present writers take the view that, if the oxide (*B*) and the ion (*C*) undergo ring-opening with nucleophilic attack at the primary carbon atom, as indicated, then there is no reason why the intermediate (*D*) should undergo ring opening

$CH_2{\cdot}CH{\cdot}CH_2X$ (OH$^+$) (*A*) $\quad$ $CH_2{\cdot}CH{\cdot}CH_3$ (O) (*B*) $\quad$ $CH_2{\cdot}CH{\cdot}CH_3$ (OH$^+$) (*C*) $\quad$ $CH_2{\cdot}CH{\cdot}CH_3$ (Cl$^+$) (*D*) $\quad$ $CH_2{=}{=}CH{\cdot}CH_3$ (Cl) (*E*)

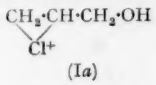
in the opposite direction. Dewar (*Discuss. Faraday Soc.*, 1947, **2**, 75; *Bull. Soc. chim.*, 1951, C 71) has realised this point; he suggests that the intermediate in the addition reaction must therefore be a π-complex (*E*). There is, however, clearly no necessity to invoke this hypothesis. It is more reasonable to assume that the intermediate in the addition reaction is an "open" carbonium ion. Stewart and VanderWerf (*J. Amer. Chem. Soc.*, 1954, **76**, 1259) recognise this point, which has also been discussed by de la Mare (in Klyne, "Progress in Stereochemistry," Butterworth, London, in the press). Below, we develop the view that this hypothesis gives a much more ready explanation of the change in orientation with structure and reagent.

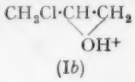
Consideration of Table (*a*) shows, that for propylene and allyl chloride, and presumably also for allyl alcohol, when a proton is the electrophilic reagent leading attack on the molecule, addition is completed entirely by attack at the secondary position. This accords with the *ortho-para*-orienting characteristics of the substituents Me, CH_2Cl, and $CH_2{\cdot}OH$ in aromatic substitutions. It is assumed, therefore, that in the absence of ready interaction between the entering group and the carbonium ionic centre, an electrophilic reagent

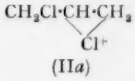
E^+ preferentially and specifically attacks the end carbon atom, to form initially the cation, $E{\cdot}CH_2{\cdot}{}^+CH{\cdot}CH_2X$.

The next point that requires consideration deals with the "neighbouring group" influence of H, Cl, and OH substituents. Winstein *et al.* (*locc. cit.*) have discussed these matters extensively, both for carbonium ions produced in unimolecular solvolyses of halides and alkyl toluene-*p*-sulphonates, and in relation to carbonium ions as intermediates in addition reactions. The hydrogen substituent participates in these reactions only in very special structural situations. The chlorine substituent provides no "driving power" assisting heterolysis. Hence when chlorine is the neighbouring group, the carbonium cation is produced initially and, when the carbonium ionic centre has been formed, interacts with the neighbouring chlorine substituent to allow retention of configuration at the carbonium ionic centre. The hydroxyl substituent contributes a quite substantial driving force assisting heterolysis; hence the interaction of a hydroxyl group with the adjacent carbonium centre must be considerably more favourable energetically than that of a chlorine substituent similarly placed.

The results described in the present paper allow comparison of behaviour of the ions $CH_2Cl{\cdot}{}^+CH{\cdot}CH_2{\cdot}OH$ and $CH_2Cl{\cdot}{}^+CH{\cdot}CH_2Cl$ which, it is presumed, are formed initially in the addition of hypochlorous acid to allyl alcohol and allyl chloride respectively. It is assumed, as has been argued above, that these ions cannot be written in the forms (I*a*), (I*b*), and (II*a*). Furthermore, they do not react by any means completely by transformation into these forms before their reaction with the nucleophilic reagent: for then

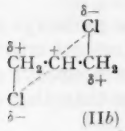

(I*a*)

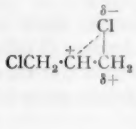

(I*b*)

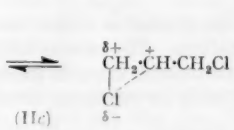

(II*a*)

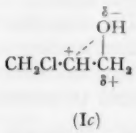
completion of the attack would involve attack on the primary carbon atom, as, for example, in the acid-catalysed ring opening of epichlorohydrin which is believed to involve (I*b*); whereas, in the addition reactions considered, a substantial part of the reaction gives the product of attack at the secondary position.

The results of the previous paper show also that the intermediate (II) cannot be completely or even largely represented in the form (II*b*) or (II*c*).


(II*b*)




(II*c*)

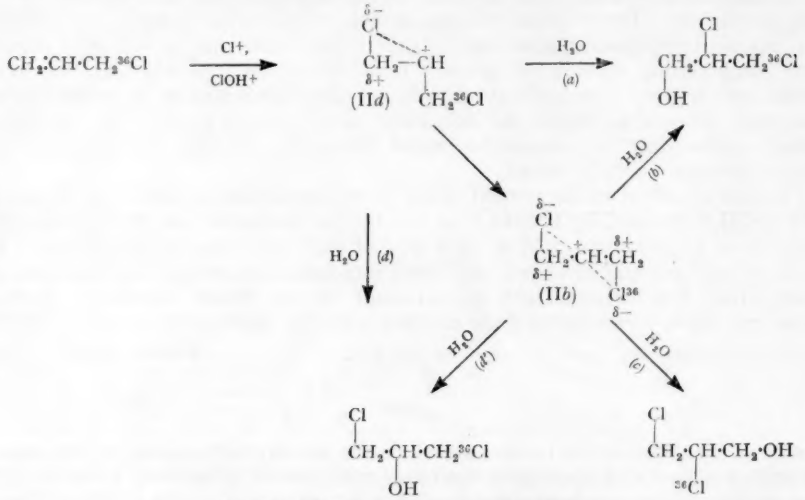

(I*c*)

Again, it is known from Winstein's work that the hydroxyl group interacts with a carbonium centre considerably more strongly than does a chlorine substituent; so that if the intermediate (I) from allyl alcohol survived long enough for the energetically preferred configuration to be assumed, the form (I*b*) or (I*c*) would be adopted and none of the monochlorohydrin produced in the reaction would have the chlorine substituent in the secondary position. In fact, 25% of the 2-chloropropane-1 : 3-diol is produced.

The above considerations restrict to some extent the possibilities which need to be considered in these addition reactions. Below is given a somewhat detailed formulation of the reaction path which may be followed in the addition of hypochlorous acid to allyl chloride.

In the formulation of (II*d*), it is implied that the entering chlorine substituent will in general be situated more favourably, for interaction with the developing carbonium ionic centre, than is the labelled chlorine substituent already present in the molecule. This seems reasonable since, for such interaction to be important, the carbon–halogen bond requires to be displaced to some extent from its usual tetrahedral position. Rotation of the CH_2Cl group would, if the life of the cation were sufficiently long, make the chlorine substituents equivalent; but it seems that reaction (*a*), with the solvent, accompanied by migration of the chlorine from the 1- to the 2-position, may occur so rapidly after the formation of the

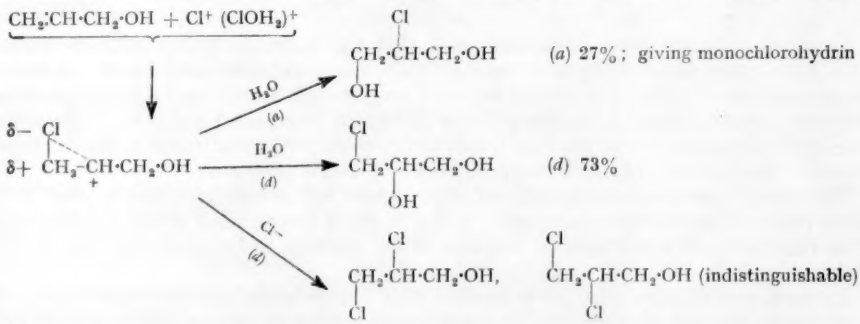
cation that a substantial part of the reaction follows this path. It is not known whether the migration of the chlorine substituent in this stage is a unimolecular or a bimolecular reaction of the cation; it is possible that the migration is synchronous with attack by the nucleophilic solvent on the 1-position. The transient formation of (II*b*) accounts for at least about 8% of the total reaction; and there is no way of knowing whether a part, if not all, of the reaction following route (*d*) in fact comes from intermediate (II*b*). Some of (II*b*) may also be formed directly from the starting materials, in the case of that fraction



(*a*) 61%; (*b*) 4%; (*c*) 4%; (*d*) (*d'*) 31%.

of the allyl chloride molecules which were conformationally arranged at the moment of attack so that the two chlorine atoms were situated symmetrically with respect to the central atom.

The situation for allyl alcohol is rather more simple, since none of the hydroxyl substituent undergoes migration. The reason why the hydroxyl substituent does not migrate, whereas the chlorine substituent does, is probably that the tendency of a hydroxyl substituent to be removed, with its electrons, from a carbon atom is much less than that of a



chlorine substituent, as is shown, for example, in the more ready S_N1 and S_N2 displacements of halides compared with alcohols. It is consistent with this view that Smith and Skyle (*loc. cit.*) record that the reaction of hypobromous acid with allyl bromide gives *ca.* 80% of 2 : 3-dibromopropan-1-ol. This suggests that still more migration is possible when the more easily displaced bromine substituent is present. Edwards and Hodges (*J.*, 1954, 761) similarly obtained from the reaction of allyl bromide with bromine acetate some 70%

of 2 : 3-dibromopropyl acetate. This was identified by infra-red measurements, but it is difficult to be certain that the isomer was entirely absent.

The amount of product formed by migration from the point of initial attack increases as the reagent is changed from HCl to ClOH to ICl. We consider this to indicate that migration depends on participation of the entering substituent as a neighbouring group, in the sense in which this term is used by Winstein and his school. In the view developed in this paper, there are two distinct modes of interaction, both of which may result in retention of configuration at the carbonium centre and hence *trans*-addition to olefinic substances. One of these is electrostatic in origin, and is of the type proposed by Cowdrey, Hughes, Ingold, Masterman, and Scott for the α-carboxylate-ion substituent (*J.*, 1937, 1252; cf. also Ingold, *op. cit.*). This type of interaction is available for the chlorine and the hydroxyl substituents, and also probably for the iodine substituent, as is shown in the formation of $CH_2I{\cdot}CHCl{\cdot}CH_3$ in predominant amount from propylene and iodine chloride. The other is, as regards bonding of one of the chlorine substituents, of the " chloronium " type. It might be intermediate between (II*b*) and the product of reaction (*b*) for example, in the above scheme for allyl chloride, provided that this reaction is unimolecular. Experiments relating to other systems and reagents are in progress with a view to testing the general applicability of these views.

We are indebted to Professors C. K. Ingold, F.R.S., and E. D. Hughes, F.R.S., for their continued encouragement and for valued discussions.

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The Chemistry of Extractives from Hardwoods. Part XVIII. The Constitution of Arjunolic Acid, a Triterpene from* Terminalia arjuna.

By F. E. KING, T. J. KING, and J. M. ROSS.

[Reprint Order No. 5561.]

Arjunolic acid, the principal extraneous constituent of the timber kumbuk (*Terminalia arjuna*), is a triterpene acid, $C_{30}H_{48}O_5$. It contains a readily lactonised olefinic bond and three alcoholic substituents, of which two constitute an α-glycol system. Pyrolysis of the acid in presence of copper caused the liberation of formaldehyde, a degradative test believed to be typical of 3 : 23-hydroxylated triterpenes, *e.g.*, bassic acid and hederagenin.

The tentative structure thus suggested for the new triterpene, *i.e.*, 2 : 3 : 23-trihydroxyolean-12-en-28-oic acid (II), was verified by degradation to a diosphenol and formaldehyde by alkaline hydrolysis of the ketone obtained through the oxidation of 18-*iso*arjunolic lactone diacetate. The diosphenol is identical with a known derivative of hederagenin (Ruzicka, Jeger, and Norymberski, *Helv. Chim. Acta*, 1944, **27**, 1185).

THE ornamental tree *Terminalia arjuna* Bedd. (*T. glabra* W. and A.), found in India, Ceylon, and Burma, yields a rich purple-brown heavy wood of fine texture superficially resembling American black walnut (*Juglans nigra*). Small quantities are available in Gt. Britain and are marketed as kumbuk. Solvent extraction of this dense and difficultly powdered wood has led to the isolation of arjunolic acid, a new trihydroxytriterpene carboxylic acid.

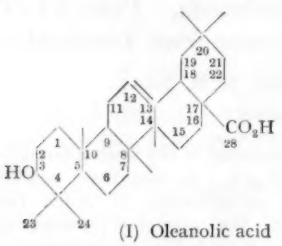
Preliminary treatment with boiling light petroleum removed a small oily fraction containing oleanolic acid (I) and " β-sitosterol." Arjunolic acid, the principal extraneous component of the wood (2½%), was obtained in the subsequent ether-extraction; owing to its low solubility prolonged treatment was necessary, the crude acid separating from the boiling solvent as a white crystalline powder. From the portion remaining in the ethereal solution traces of ellagic acid were isolated.

* Part XVII, *J.*, 1954, 1399.

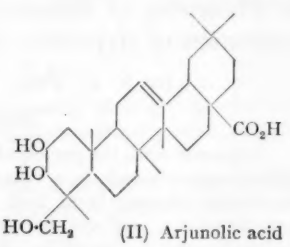
Arjunolic acid has the molecular formula $C_{30}H_{48}O_5$ and responds to the usual qualitative tests for triterpenes. Experiments described in this memoir unequivocally establish the constitution of the acid as 2 : 3 : 23-trihydroxyolean-12-en-28-oic acid (II), thus superseding the putative structure already published (*Chem.* and *Ind.*, 1953, 1325).

The triterpene alkali salts are sparingly soluble in water, but suspensions of the acid in ethanol dissolve on the addition of aqueous sodium hydroxide; moreover, the carboxyl function is readily discerned by the formation with diazomethane or methyl sulphate–alkali, but not with methanolic hydrochloric acid, of a crystalline (mono)methyl ester. As with other triterpene acids, drastic conditions of hydrolysis are necessary to recover the acid from its ester. The crystalline ethyl and *p*-nitrobenzyl esters also served to characterise the acid. The hydroxylic character of the remaining three oxygen atoms was shown by the preparation of arjunolic acid triacetate and of methyl arjunolate triacetate which, however, were not obtained crystalline.

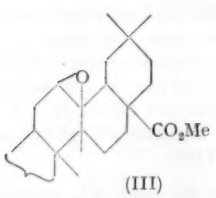
Arjunolic acid resisted catalytic hydrogenation over platinum oxide, but was shown to be unsaturated by means of tetranitromethane. The degree of unsaturation was determined by oxidation of the acid or of its derivatives with perphthalic acid and analysis of the oxidation products. Methyl arjunolate, for example, afforded a simple epoxide (III), m. p. 174—175°, which, being without action on tetranitromethane, contained no olefinic bond. Methyl arjunolate thus resembles methyl oleanolate (acetate) (Picard and Spring, *J.*, 1940, 1387) and differs from the corresponding α-amyrin derivatives which under comparable conditions are inert to peroxidation. Like the oleanolate oxide (Picard and Spring, *loc. cit.*), methyl arjunolate oxide is isomerised by mineral acid to a dihydro-oxo-compound (IV), m. p. 191—192°, more easily obtained, however, from methyl arjunolate triacetate by the action of hot hydrogen peroxide–acetic acid followed by alkaline hydrolysis.



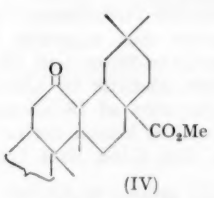
(I) Oleanolic acid



(II) Arjunolic acid



(III)



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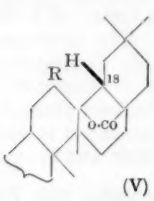


(V)

The products (III) and (IV) are well differentiated by their infra-red absorption spectra. Thus, methyl arjunolate and methyl epoxyarjunolate in carbon tetrachloride solutions exhibit a single carbonyl band, at 1724 and 1723 cm.$^{-1}$ respectively, due to the methoxycarbonyl group. On the other hand, the spectrum of methyl dihydro-oxoarjunolate (determined in Nujol suspension owing to the low solubility in carbon tetrachloride) has two carbonyl bands, at 1683 and 1722 cm.$^{-1}$, corresponding respectively to saturated keto- and ester-carbonyl groups. We are indebted to Dr. G. D. Meakins, University of Manchester, for these and other infra-red absorption determinations recorded in this paper, which were undertaken through the kindness of Professor E. R. H. Jones, F.R.S.

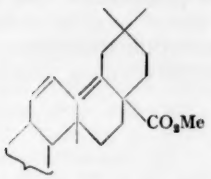
The position of the double bond with respect to the carboxyl group was deduced from the peroxidation of arjunolic acid to a hydroxy-lactone (V; R = OH) and from the ready formation of a highly crystalline bromo-lactone (V; R = Br) of which a triacetyl derivative

was prepared. Easy lactonisation is characteristic of carboxylic acids of the β-amyrin series having a double bond γδ to the carboxyl group (see, for example, Jeger, *Fortschr. Chem. Org. Naturstoffe*, 1950, **7**), and it was accordingly inferred that arjunolic acid is unsaturated at the 12-position as in oleanolic acid.

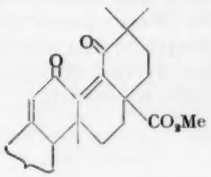
With boiling methanolic potassium hydroxide the bromo-lactone was converted into a saturated neutral compound, $C_{31}H_{50}O_6$, m. p. 250—252°, which like the epoxide of m. p. 174—175° was isomerised by mineral acid to the dihydro-oxoarjunolate (IV). An isomeric neutral product of higher melting point than the normal epoxide has been observed in the methanolic alkaline hydrolysis of oleanolic bromo-lactone (Kitisato, *Acta Phytochem. Tokyo*, 1933, **7**, 169; *Chem. Centr.*, 1934, I, 2765), but its structure does not appear to have been ascertained. Light absorption measurements on the compound of m. p. 250—252° disclose a carbonyl band at 1724 cm.$^{-1}$ corresponding to the ester-carbonyl band of methyl arjunolate and of methyl epoxyarjunolate and differing from the carbonyl absorption (1779 cm.$^{-1}$) of the bromo-lactone. The absence of a true carbonyl group is confirmed by the ultra-violet absorption spectrum which lacks the weak carbonyl peak at *ca.* 280 mμ. From these data it is evident that the intermediate of m. p. 250—252° is a stereoisomeride of methyl epoxyarjunolate, m. p. 174—175°, and it is concluded that a similar relation exists between the analogous derivatives of oleanolic acid.

The production of isomeric epoxide esters is to be expected from mechanistic considerations. In the hydrolysis of arjunolic bromo-lactone, the formation of the methoxycarbonyl group, which results from the attack of methoxide ion on the lactone ·CO–O· bond, will leave a negatively charged oxygen at $C_{(13)}$. The configuration of this oxygen atom, which is axial and therefore β, will not be affected by the ensuing elimination of Br^- and will consequently remain unchanged in the resulting oxide ring. Conversely, it can be deduced that the preparation of epoxides by peroxidation of the 12 : 13-double bond will afford products in which the added oxygen has the opposite (α-)configuration. This follows from the configuration assumed by the 12-hydroxyl group in the hydroxyoleanolic acid obtained in this way from oleanolic acid, which Barton and Holness (*J.*, 1952, 78) regard as axially and therefore α-bonded. Since it may be accepted that this substituent is derived from the rearrangement of an initially formed epoxy-acid, a process not involving the $C_{(12)}$–O bond, the epoxide ring also will have the α-configuration, *i.e.*, it is the converse of that originating from the bromo-lactone.

As is usual in the fission of lactones with alcoholic alkali, the use of potassium hydroxide in ethanol instead of the methanolic reagent resulted in the formation of an acidic product from the bromo-lactone (V; R = Br), which with diazomethane yielded methyl dihydro-12-oxoarjunolate (IV).



(VI)



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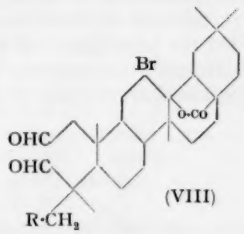


(VIII)

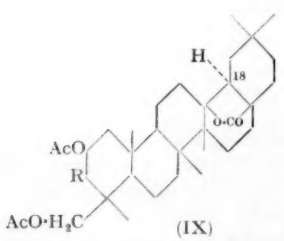
A further resemblance between the new triterpene and oleanolic acid was observed in the reaction of methyl arjunolate triacetate with selenium dioxide. Treatment with 0·5 mol. of the reagent in boiling acetic acid and de-acetylation of the product afforded a crystalline diene (VI) having the characteristic triple ultra-violet absorption bands ($\lambda_{max.}$ 243·5, 251, and 260·5 mμ) of a triterpene 11 : 13(18)-diene (Ruzicka and Jeger, *Helv. Chim. Acta*, 1942, **25**, 775; Barton and Holness, *loc. cit.*). The oxidation corresponds to that of methyl oleanolate acetate (Ruzicka, Grob, and van der Sluys-Veer, *Helv. Chim. Acta*, 1939, **22**, 788) and the change is accompanied by the typical large negative shift in optical rotatory power. More vigorous oxidation of the oleanolate with larger quantities of selenium

dioxide gave a 10 : 13(18)-diene-12 : 19-dione with strong absorption in the ultra-violet ($\lambda_{max.}$ 275 mμ, ε 12,500) (*idem, loc. cit.*; Ruzicka, Jeger, and Winter, *ibid.*, 1943, **26**, 265) and, although non-crystalline, the material similarly obtained from methyl arjunolate triacetate was estimated from its light absorption ($\lambda_{max.}$ 275 mμ, ε 6800) to contain approximately 50% of the comparable diene-dione (VII).

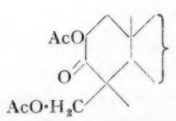
The evidence of these preliminary experiments suggested that arjunolic acid was a dihydroxy-derivative of oleanolic acid. Indications as to the disposition of the hydroxyl groups was afforded by the quantitative oxidation of methyl arjunolate with sodium periodate, the disappearance of 1 mol. of the reagent establishing the existence of a 1 : 2-glycol unit. Arjunolic acid was likewise readily oxidised by lead tetra-acetate but without the formation of any purifiable product. On the other hand, arjunolic bromo-lactone with this reagent yielded a crystalline material of which the elementary composition was in agreement with its representation as a dicarbonyl compound, presumably (VIII; R = H), but the 2 : 4-dinitrophenylhydrazone was amorphous. The action of zinc dust and acetic acid on the supposed dialdehyde (VIII) effected debromination and cleavage of the lactone ring, and a crystalline acid was obtained which was unsaturated (tetranitromethane) and gave an amorphous 2 : 4-dinitrophenylhydrazone.

Important information concerning the situation of the hydroxyl substituents was acquired from experiments on the pyrolysis of arjunolic acid. When heated with copper catalysts at 270—290° the acid gave small but consistent amounts of formaldehyde, identified by means of the dimedone derivative. A similar decomposition yielding formaldehyde has been observed with other triterpenes, *e.g.*, bassic acid and hederagenin, and it is regarded as typical of the 3 : 23-diol system in the triterpene series (Tsuda and Kitagawa, *Ber.*, 1938, **71**, 1604). If accepted, this evidence, together with that afforded by the periodate and tetra-acetate oxidations, at once establishes the orientation of the three hydroxyl groups in arjunolic acid. An attempt was made to confirm the presence of neighbouring hydroxyl substituents, *e.g.*, as in the case of the 3 : 23-diol grouping in hederagenin, by the preparation of an *iso*propylidene derivative, but the product could not be obtained crystalline.

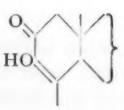
The foregoing deductions were confirmed beyond doubt by developments which arose from a study of the lactonisation of arjunolic acid. Under conditions devised by Winterstein and Wiegand (*Z. physiol. Chem.*, 1931, **199**, 46), namely, treatment at room temperature with a mixture of hydrobromic and acetic acids, a lactone triacetate was obtained. To this derivative the 18-*iso*(α-)structure (IX; R = OAc) is ascribed since it is known that similar reagents effect the translation of the D–E ring junction in oleanolic acid from the *cis* to *trans* (Barton and Holness, *loc. cit.*). The very high yield of acidic material remaining when arjunolic acid was treated with cold hydrochloric and acetic acids, conditions in which acids of the 18-*iso*(α-)series undergo almost total lactonisation, excluded the possibility that the original triterpene already possessed the *iso*-configuration. The *iso*lactone triacetate was easily deacetylated with alkalis, and the resulting trihydroxy-lactone was characterised by a crystalline tribenzoate.



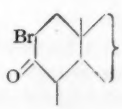
(IX)



(X)



(XI)



(XII)

With boiling hydrochloric and acetic acids (Winterstein and Stein, *Z. physiol. Chem.*, 1931, **200**, 64) a new derivative was obtained which proved to be a lactone diacetate, later shown to be (IX; R = OH). Oxidation of the diacetate with chromic anhydride–acetic acid gave 3-oxo-18-*iso*(α-)arjunolic lactone 2 : 23-diacetate (X) which was then subjected

to alkaline hydrolysis. Analyses of the crystalline product, m. p. *ca.* 320°, were anomalous and implied that in addition to the removal of acetyl groups a net loss of CH_4O had occurred. Moreover, re-acetylation of the compound, m. p. 320°, afforded a new derivative, m. p. 274—275°, analysis of which confirmed the decreased molecular weight. The nature of the hydrolysis product was indicated by the relative ultra-violet absorptions of the compound ($\lambda_{max.}$ 281 mμ, ε 12,000) and its acetate ($\lambda_{max.}$ 246 mμ, ε 11,800) which indicate a diosphenol structure, *i.e.*, (XI), and in agreement with this the compound of m. p. 320° had a ferric reaction. The behaviour of the oxoarjunolic lactone diacetate is therefore reminiscent of that of icterogenin (Barton and de Mayo, *J.*, 1954, 887) which under the influence of alkali sustains loss of the methylol grouping at $C_{(4)}$, and from the cautious hydrolysis of the oxoarjunolic lactone diacetate (X) formaldehyde was subsequently isolated as its dimedone derivative.

The production of the diosphenol (XI) from (X) requires the removal also of two hydrogen atoms, either by atmospheric oxidation or, since the compound is obtained (27%) even in the total absence of air, by a disproportionation. An analogy for the reaction is, in fact, found in the spontaneous oxidation of 2-bromohedragone lactone (XII) during alkaline hydrolysis, a method whereby the diosphenol (XI) was originally prepared (Ruzicka, Jeger, and Norymberski, *loc. cit.*). A small amount of the derivative (XI) was also obtained by direct oxidation of the 18-*iso*arjunolic lactone with chromic acid, elimination of the 23-carbon atom presumably occurring as carbon dioxide through the decarboxylation of an intermediate β-keto-acid. This is comparable with the oxidation of methyl asiatate to a diosphenol (Polonsky, *Compt. rend.*, 1951, **233**, 93) and is a result to be expected from the very close resemblance of the two triterpenes.

The identification of the diosphenol (XI) as that earlier obtained from hederagenin also determines the detailed stereochemical structure of arjunolic acid with, of course, the exception of the spatial relation of the three hydroxyl groups. The fluency of reaction exhibited by these substituents, both in the formation and hydrolysis of derivatives, implies that the secondary 2- and 3-hydroxyl groups are *trans*-equatorial and therefore respectively α and β. Further evidence as to the configuration of these and of the 23-hydroxymethyl group is being sought, *e.g.*, by partial synthesis of the triterpene.

Experimental

Except where otherwise stated, specimens for analysis were dried for 2 hr. at 120°/0·1 mm. Ethanol solutions were used for ultra-violet light absorption measurements, and chloroform for the optical rotations.

Solvent Extraction of Terminalia arjuna *Heartwood.*—Continuous extraction of the powdered wood (4 kg.) with boiling light petroleum (b. p. 60—80°) for 18 hr. afforded a pale yellow solution containing suspended gelatinous solid (2 g.) which was collected and crystallised from methanol (norite). After purification as the potassium salt (cf. Dodge, *J. Amer. Chem. Soc.*, 1918, **40**, 1917) and further repeated crystallisation (from methanol), oleanolic acid (35 mg.) was obtained as needles, m. p. 306—308° (lit., 310°) (Found, in a specimen dried at 150°/0·1 mm.: C, 78·7; H, 10·7. Calc. for $C_{30}H_{48}O_3$: C, 78·9; H, 10·6%); the methyl ester, prepared from methyl sulphate–methanolic alkali, had m. p. 203° (Found: C, 78·6; H, 11·0; OMe, 6·5. Calc. for $C_{31}H_{50}O_3$: C, 79·1; H, 10·7; OMe, 6·6%), and the acetate m. p. 262° (Found: C, 77·1; H, 10·1; OAc, 9·7. Calc. for $C_{32}H_{50}O_4$: C, 77·1; H, 10·1; OAc, 8·6%).

The orange-red oil (10·3 g., 0·3%) obtained by evaporation of the clear petroleum solution slowly deposited solid which yielded "β-sitosterol" (0·1 g.), m. p. 136°, after numerous crystallisations from methanol; chromatography of the oil in benzene on alumina and elution with ether–methanol (1 : 1) isolated a further quantity, m. p. 137—138°, which was characterised by the acetate, m. p. 125—126° (Found: C, 81·6; H, 10·7; OAc, 10·0. Calc. for $C_{31}H_{52}O_2$: C, 81·5; H, 11·4; OAc, 9·4%), and benzoate, m. p. 145—146° (Found: C, 82·8; H, 10·4. Calc. for $C_{36}H_{54}O_2$: C, 83·3; H, 10·5%).

Further extraction with boiling ether for 48 hr. produced a colourless crystalline deposit (104 g., 2·6%) consisting of arjunolic acid, m. p. 315—325°. The yellow supernatant liquid was removed and evaporated, and the residue heated with hot acetic acid (15 c.c.); the remaining solid then crystallised from pyridine in minute pale yellow needles, soluble in aqueous sodium hydroxide to a deep yellow solution, and giving a blue-black precipitate with ferric

chloride and other reactions of ellagic acid, *e.g.*, Griessmeyer and Alvarez tests (*Abstr.*, 1907, **92**, ii, 143).

Arjunolic Acid (II).—The product, m. p. 315—325°, was first subjected to Soxhlet extraction with acetone and thereafter recrystallised by dissolving it in a large volume of this solvent (1 g. in 175 c.c.), the solution then being concentrated tenfold. Pure *arjunolic acid* formed minute plates, m. p. 337—340°, $[\alpha]_D^{19}$ +63·5° (*c*, 0·51 in EtOH) (Found: C, 74·2, 73·9; H, 9·9, 9·6. $C_{30}H_{48}O_5$ requires C, 73·7; H, 9·9%). The acid is readily soluble in acetic acid, dioxan, pyridine, and 2-ethoxyethanol, but slightly or very slightly soluble in other organic solvents. It is not dissolved by aqueous carbonates or, apparently, by aqueous sodium hydroxide owing to the sparing solubility of its sodium salt, best obtained as long silky needles by treatment of an alcoholic solution of the acid with the concentrated aqueous alkali. Its solution in sulphuric acid was yellow changing to red; Liebermann–Burchardt reaction, pink to brown; Tschugaieff reaction, orange, red, red-brown. A solution of the acid in tetranitromethane was faintly yellow.

Arjunolic acid was esterified (yield 90%) when suspended in methanol and treated with ethereal diazomethane, and by the action of methyl sulphate on the acid in methanolic sodium or potassium hydroxide. *Methyl arjunolate* crystallised from methanol in needles, m. p. *ca.* 209—211°; absorbed from benzene solution on alumina, eluted with ether–methanol (3 : 1), and dried at 120°/0·1 mm., it had m. p. 215—216° followed by resolidification and final m. p. 248—250°. After prolonged drying (10 hr.) at 200°, it had m. p. 248—250° with slight previous sintering, $[\alpha]_D^{20}$ +68° (*c*, 1·65) (Found, in a specimen briefly dried at 225°/20 mm.: C, 73·7; H, 10·2; OMe, 6·4. $C_{31}H_{50}O_5$ requires C, 74·1; H, 10·0; OMe, 6·2%). Refluxing in 10% methanolic potassium hydroxide for 3 hr. resulted in almost quantitative recovery of the ester, m. p. 215—216°.

The *ethyl* ester, prepared from a solution of arjunolic acid in aqueous-ethanolic sodium hydroxide and ethyl sulphate, crystallised from aqueous ethanol in needles, m. p. 202—203°. The product appeared to be solvated and was prepared for analysis by brief drying above the m. p. (Found: C, 74·0; H, 9·9. $C_{32}H_{52}O_5$ requires C, 74·4; H, 10·1%), $[\alpha]_D^{20}$ +58° (*c*, 1·58).

Refluxing the acid with *p*-nitrobenzyl bromide in methanolic potassium hydroxide for 1 hr. gave the p-*nitrobenzyl* ester which crystallised from aqueous ethanol in minute leaflets, m. p. 236—238°, $[\alpha]_D^{19}$ +34° (*c*, 0·91) (Found, in a specimen dried at 150°/0·1 mm.: C, 71·6; H, 8·4; N, 2·2. $C_{37}H_{53}O_7N$ requires C, 71·2; H, 8·6; N, 2·25%).

The *acid triacetate* was obtained from arjunolic acid by treatment with acetic anhydride–pyridine or –perchloric acid at room temperature or with acetic anhydride–sodium acetate (heating), but it formed a colourless amorphous powder which did not crystallise (Found: C, 70·0; H, 9·0; OAc, 18·0. $C_{36}H_{54}O_8$ requires C, 70·3; H, 8·9; 3OAc, 21·0%). Esterification of the triacetate, or acetylation of methyl arjunolate, gave the amorphous *methyl arjunolate triacetate* (Found: C, 69·9; H, 9·0. $C_{37}H_{56}O_8$ requires C, 70·7; H, 9·0%).

Methyl 12 : 13-*Epoxyarjunolate* (III).—Methyl arjunolate (0·1064 g.) in dioxan (5 c.c.) was mixed with monoperphthalic acid in ether (5 c.c.; 0·57N), and the solution made up to 25 c.c. with ether and set aside at 0°. Samples (5 c.c.) were removed after 24, 44, and 145 hr., iodometric titrations indicating a consumption of 0·34, 0·69, and 1·09 mols. respectively of the per-acid.

Methyl arjunolate (3·24 g.) in ether–dioxan (3 : 1; 200 c.c.) was then treated with ethereal monoperphthalic acid (35 c.c.; 0·57N), and after 14 days at 0—2° the mixture was washed with N/4-sodium hydroxide and dried (K_2CO_3). Evaporation of the solvent and crystallisation from methanol gave *methyl* 12 : 13-*epoxyarjunolate* (3·0 g.) in rosettes of needles, m. p. 174—175°, $[\alpha]_D^{19}$ +36° (*c*, 1·92) (Found: C, 71·7; H, 9·5; OMe, 6·0. $C_{31}H_{50}O_6$ requires C, 71·8; H, 9·7; OMe, 6·0%).

Methyl 12 : 13-*Epoxyarjunolate Triacetate*.—Methyl arjunolate triacetate (1·1 g.), dissolved in ether (20 c.c.), was treated with monoperphthalic acid (50 c.c.; 0·3N) at 0—2° for 12 days. By working up of the product in the usual way, a colourless amorphous *epoxide* (1·12 g.) was obtained (Found: C, 69·0; H, 8·9. $C_{37}H_{56}O_9$ requires C, 68·9; H, 8·7%).

Methyl Dihydro-12-*oxoarjunolate* (IV).—Methyl arjunolate triacetate (1·0 g.) in acetic acid (30 c.c.) was treated on a steam-bath with aqueous hydrogen peroxide (2 c.c.; 30%), added in ½ hr. After being further heated for 2 hr., the solution was poured into water, and the amorphous product collected and hydrolysed with boiling methanolic potassium hydroxide. Working up in the usual way gave *methyl dihydro*-12-*oxoarjunolate* (0·6 g.) which crystallised from aqueous methanol in long flattened needles, m. p. 191—192°, $[\alpha]_D^{20}$ +30° (*c*, 1·45) (Found: C, 71·7; H, 9·6; OMe, 5·7. $C_{31}H_{50}O_6$ requires C, 71·8; H, 9·7; OMe, 6·0%).

The dihydro-oxoarjunolate was also obtained when methyl epoxyarjunolate or its acetate

was heated for 2—6 hr. on a steam-bath in acetic acid containing a small amount of concentrated hydrochloric acid, the amorphous acetate being hydrolysed with alkali. However, amorphous material produced during the rearrangement of the epoxide was wasteful to remove and the hydrogen peroxide–acetic acid method is preferable.

12-Hydroxyarjunolic Lactone (V; R = OH).—A dioxan solution of arjunolic acid (0·1036 g.), and monoperphthalic acid in ether (5 c.c.; 0·49N), was made up to 25 c.c.; titres after 24, 44, and 145 hr. were equivalent to 0·18, 0·48, and 1·08 mols. of per-acid consumed. Oxidation on a larger scale (3·3 g.) gave, after washing with 0·1N-sodium hydroxide, *12-hydroxyarjunolic lactone* (2·2 g.) as leaflets (from aqueous methanol), m. p. 278—280°, $[\alpha]_D^{20}$ +28·5° (*c*, 0·76) (Found: C, 71·7; H, 9·6. $C_{30}H_{48}O_6$ requires C, 71·4; H, 9·6%).

The *triacetate* was similarly obtained from arjunolic acid triacetate. After removal of acidic material, it separated from a concentrated ethereal solution, and when recrystallised from aqueous methanol formed stout prisms, m. p. 179—180°, $[\alpha]_D^{19}$ +20° (*c*, 1·20) (Found: C, 68·0; H, 8·4. $C_{36}H_{54}O_9$ requires C, 68·5; H, 8·6%).

Arjunolic Bromo-lactone (V; R = Br).—A solution of arjunolic acid (5 g.) and sodium acetate (10 g.) in acetic acid (100 c.c.; 90%) was stirred during the dropwise addition of 4% bromine–acetic acid (100 c.c.), and after 1 hr. the mixture was poured into water (800 c.c.) containing sodium thiosulphate (10 g.). The precipitate was recrystallised from methanol (norite), the *bromo-lactone* separating in prisms (3·5 g.), m. p. 240—244° (decomp.), $[\alpha]_D^{19}$ +55° (*c*, 1·24) (Found: C, 63·6; H, 8·2; Br, 14·6. $C_{30}H_{47}O_5Br$ requires C, 63·5; H, 8·3; Br, 14·1%). With boiling acetic anhydride–pyridine for ½ hr. it gave the *bromo-lactone triacetate* which crystallised from methanol in large irregular prisms, m. p. 182—183°, $[\alpha]_D^{20}$ +54° (*c*, 2·46) (Found: C, 62·1; H, 7·8. $C_{36}H_{53}O_8Br$ requires C, 62·3; H, 7·7%).

When the bromo-lactone (0·5 g.) in acetic acid (15 c.c.) was treated with zinc dust (3·5 g.) on a steam-bath for 3 hr., arjunolic acid was regenerated, and after precipitation from the filtered solution with water and crystallisation from methanol it had m. p. and mixed m. p. 336—338° (Found: C, 74·0; H, 9·6%). The acid was also obtained by reduction with sodium amalgam in boiling ethanol.

Hydrolysis of Arjunolic Bromo-lactone.—(i) The bromo-lactone (1·1 g.) was heated under reflux with 10% methanolic potassium hydroxide during 3 hr. *Methyl isoepoxyarjunolate* was precipitated by pouring the solution into water, and it crystallised from aqueous methanol as long thin rods or needles (0·8 g.), m. p. 250—252° with extensive sintering at 240°. Drying at room temperature gave a *hydrate* (Found: C, 69·5; H, 9·8. $C_{31}H_{50}O_6,H_2O$ requires C, 69·4; H, 9·7%); the anhydrous material was obtained after drying at 150°/0·1 mm. and had $[\alpha]_D^{20}$ +48° (*c*, 1·48) (Found: C, 71·5; H, 9·8; OMe, 6·0. $C_{31}H_{50}O_6$ requires C, 71·8; H, 9·7; OMe, 6·0%).

Treatment of this compound in chloroform solution at room temperature with a stream of hydrogen chloride during ½ hr. resulted in a quantitative conversion into methyl dihydro-12-oxo-arjunolate, m. p. and mixed m. p. 191—192°.

(ii) Hydrolysis of the bromo-lactone (0·5 g.) with ethanolic potassium hydroxide gave an amorphous material almost completely soluble in hot 0·1N-sodium hydroxide containing 10% of methanol. The product obtained by acidification of the alkaline solution could not be crystallised, but on treatment with diazomethane in ether formed methyl dihydro-12-oxo-arjunolate (0·24 g.), m. p. and mixed m. p. 191—192°.

Methyl 11 : 13(18)-*Dehydroarjunolate* (VI).—Methyl arjunolate triacetate (1·4 g.) was heated with pure selenium dioxide (0·125 g.) in boiling acetic acid (50 c.c.) for 17 hr. The product, precipitated when the mixture was poured into water, was heated under reflux for 2 hr. with 5% methanolic potassium hydroxide. *Methyl* 11 : 13(18)-*dehydroarjunolate* was obtained by addition of water, and it crystallised from methanol in colourless laths, m. p. 250—251°, $[\alpha]_D^{20}$ −153° (*c*, 1·49) (Found, in a specimen dried at 150°/0·1 mm.: C, 74·6; H, 9·6. $C_{31}H_{48}O_5$ requires C, 74·6; H, 9·7%). Light absorption: max. 243·5, 251, and 260 mμ; ε 21,400, 24,500, and 15,000. Barton and Holness (*loc. cit.*) record for methyl dehydro-oleanolate acetate, max., 242, 252, and 261 mμ and ε 25,500, 29,100, and 18,900 respectively.

Methyl arjunolate triacetate was also oxidised with excess of selenium dioxide during 17 hr., and the product fractionated on a column of alumina. Ether–benzene (1 : 1) eluted an amorphous acetate which when hydrolysed yielded a further small amount of the diene. Hydrolysis of the fraction eluted by ether gave a straw-coloured gum with light absorption max. at 275 mμ (ε 6800).

Oxidation of Methyl Arjunolate with Sodium Periodate.—An alcoholic solution of methyl arjunolate (0·205 g.) was treated with aqueous sodium periodate (10 c.c.; 0·092N), alcohol being

added to make up 50 c.c. The mixture was kept at 18° screened from light, and portions (10 c.c.) were removed after ¼, 1, 3½, and 20 hr. Estimation of excess of periodate with standard sodium arsenite in the usual way showed the oxidation respectively of 40, 70, 86, and 97% of a 1 : 2-glycol unit.

Oxidations with Lead Tetra-acetate.—(i) *Arjunolic acid.* Warm acetic acid solutions of lead tetra-acetate (11 g. in 200 c.c.) and of arjunolic acid (10 g. in 100 c.c.) were mixed (34°) and set aside at room temperature for 18 hr. Excess of tetra-acetate was destroyed with ethylene glycol and the mixture poured into water (1·5 l.). The precipitate was collected and dissolved in ether (300 c.c.), and the solution extracted with 1% aqueous sodium hydroxide.

The *acid* thus isolated was an amorphous solid (5·4 g.), m. p. 223—225° (Found : C, 74·5; H, 9·5. $C_{30}H_{46}O_5$ requires C, 74·1; H, 9·5%), which was unaffected by heating in boiling xylene. The residue undissolved by the alkali was a powder (2·36 g.) which could not be crystallised.

(ii) *Arjunolic bromo-lactone.* Arjunolic bromo-lactone (4·45 g.) was oxidised with lead tetra-acetate as for arjunolic acid, and the acidic fraction (0·2 g.) extracted from an ethereal solution of the product with excess of 0·1% sodium hydroxide. The neutral *aldehydo-lactone* crystallised from methanol in leaflets (3·75 g.), m. p. 211—213° raised by recrystallisation to m. p. 222°, $[\alpha]_D^{20}$ +93° (*c*, 1·10) (Found : C, 63·8; H, 8·3; Br, 13·6. $C_{30}H_{45}O_5Br$ requires C, 63·7; H, 8·0; Br, 14·2%). It yielded an amorphous yellow precipitate with 2 : 4-dinitrophenylhydrazine sulphate in ethanol.

A solution of the compound, m. p. 222° (1·05 g.), in acetic acid (30 c.c.) was heated on a steam-bath with zinc dust (7·0 g.). A stream of nitrogen passing through the reaction vessel remained carbon dioxide-free throughout the 2½ hours' heating. The solid precipitated from the filtered solution was dissolved in ether which was then extracted with 1% aqueous sodium hydroxide. The *acid* thus isolated (0·77 g.) crystallised from aqueous methanol in needles, m. p. 251° (decomp.) after sintering at 235°, $[\alpha]_D^{20}$ +152° (*c*, 0·76) (Found : C, 74·3; H, 9·4. $C_{30}H_{46}O_5$ requires C, 74·0; H, 9·5%), and gave an amorphous yellow derivative with methanolic 2 : 4-dinitrophenylhydrazine sulphate.

Pyrolysis of Arjunolic Acid.—A mixture of arjunolic acid (1 g.) and finely divided copper (5 g.) was heated in a metal-bath at 270—290° for 1 hr., and the evolved gases were passed into saturated aqueous dimedone. After a further 1 hr. the precipitate (60 mg.) was collected and when crystallised from methanol it had m. p. 188—189° alone or mixed with formaldehyde dimedone derivative.

18-iso(α-)*Arjunolic Lactone.*—Arjunolic acid (5 g.) was dissolved in hydrogen bromide–acetic acid (50 c.c. of 50%) and after 48 hr. at room temperature the brown solution was poured into water. The solid which separated crystallised from methanol in well-defined plates (4·8 g.) consisting of *triacetyl*-18-iso(α-)*arjunolic lactone*, m. p. 265—266°, $[\alpha]_D^{19}$ +12° (*c*, 3·15) (Found : C, 70·2; H, 8·9. $C_{36}H_{54}O_8$ requires C, 70·3; H, 8·9%). Hydrolysis for ¼ hr. at 100° or for 1 hr. at room temperature with varying quantities of aqueous-alcoholic alkali invariably gave 18-iso(α-)*arjunolic lactone* which originally crystallised from aqueous methanol in felted needles but later spontaneously changed to the more stable form of compact leaflets, m. p. *ca.* 350° (decomp.), $[\alpha]_D^{20}$ +6° (c, 1·05) (Found : C, 73·8; H, 10·0. $C_{30}H_{48}O_5$ requires C, 73·7; H, 9·9%).

With benzoyl chloride–pyridine overnight at room temperature the lactone afforded a *tribenzoate* which crystallised from methanol in needles, m. p. 284—285°, $[\alpha]_D^{19}$ +61° (*c*, 0·93) (Found : C, 76·8; H, 7·2. $C_{51}H_{60}O_8$ requires C, 76·5; H, 7·5%). The lactone and its acetate gave no perceptible colour with tetranitromethane.

18-iso(α-)*Arjunolic Lactone Diacetate* (IX; R = OH).—A mixture of arjunolic acid (5 g.), concentrated hydrochloric acid (35 c.c.), and acetic acid (75 c.c.) was heated under reflux for 17—24 hr. The solid obtained by pouring the solution into water was collected, dried, and triturated with ether (20 c.c.). The crystalline material remaining undissolved gave 18-iso-(α-)*arjunolic lactone diacetate* (yield normally 15—20% but on one occasion 60%) when crystallised from methanol as leaflets, m. p. 285—286°, $[\alpha]_D^{20}$ −3·5° (*c*, 1·26) (Found : C, 71·2; H, 9·1; Ac, 14·7. $C_{34}H_{52}O_7$ requires C, 71·3; H, 9·1; Ac, 15%). The diacetate was colourless in tetranitromethane.

The lactone diacetate was obtained by the action of boiling hydrochloric acid–acetic acid (1 : 2) (*a*) on 18-*iso*(α-)arjunolic lactone for 2 hr. (yield 10—20%), m. p. 280—283°, and (*b*) on the lactone triacetate for 15 min. (yield 10%), m. p. 279—282°. Partial hydrolysis of the triacetate with alkali, even with only 1 equiv. of alkali, invariably gave the trihydroxy-lactone. Conversely, acetylation of the trihydroxy-lactone with acetic anhydride (2 mols.)–pyridine-afforded the triacetate as the sole purifiable product.

Diacetyloxo-18-iso*arjunolic Lactone* (X).—The arjunolic lactone diacetate (0·8 g.) in acetic

acid (50 c.c.), mixed with chromium trioxide (0·16 g.), was set aside at room temperature overnight. The excess of chromic anhydride was then decomposed with methanol, and the solution poured into water. The resulting *diacetyloxo*-18-iso*arjunolic lactone* (0·66 g.) crystallised from methanol in long leaflets, m. p. 261°, $[\alpha]_D^{19}$ +40° (*c*, 1·48) (Found: C, 71·7; H, 8·9. $C_{34}H_{50}O_7$ requires C, 71·6; H, 8·8%).

3 : 13-*Dihydroxy*-2-*oxo*-23-*norolean*-3-*en*-28-*oic Lactone* (XI).—(i) Diacetyloxo-18-*iso*arjunolic lactone (0·5 g.) was hydrolysed with boiling methanolic potassium hydroxide (20 c.c.; 10%). The product obtained by pouring the solution into dilute hydrochloric acid was crystallised from a large volume of ethanol and then from chloroform–methanol, forming leaflets (60 mg.), m. p. *ca.* 320° (decomp.), $[\alpha]_D^{19}$ +77° (*c*, 1·05) (Found: C, 76·9; H, 9·0. Calc. for $C_{29}H_{42}O_4$: C, 76·6; H, 9·2%). Light absorption in dioxan: max. 281 mμ; ε 12,000. The diosphenol formed a pale cream potassium salt, and in ethanol with a trace of ferric chloride gave a violet colour, becoming green with excess of the reagent. Ruzicka, Jeger, and Norymberski (*loc. cit.*) record for the substance prepared from hederagenin, m. p. (variable) 325—326°, $[\alpha]_D$ +73·4° to +88·7°; $\lambda_{max.}$ (in dioxan) 280 mμ, ε 11,000, violet ferric colour. A specimen from this source was without effect on the m. p.

With cold pyridine–acetic anhydride the acetate was obtained, leaflets (from methanol), m. p. and mixed m. p. 274—275°, $[\alpha]_D^{19}$ +86° (*c*, 0·84) (Found: C, 74·9; H, 8·9. Calc. for $C_{31}H_{44}O_5$: C, 75·0; H, 8·9%). Light absorption: max. 246 mμ, ε 12,800. Ruzicka *et al.* (*loc. cit.*) record m. p. 272—273°, $[\alpha]_D$ +87°; $\lambda_{max.}$ 246 mμ, ε 12,000.

(ii) Diacetyloxo-18-*iso*arjunolic lactone (0·7 g.) in ethanol (100 c.c.) was mixed with N-sodium hydroxide (5 c.c.) and set aside in a closed flask under nitrogen. Next day the solution was acidified with aqueous sulphuric acid and diluted to 150 c.c. The precipitate was collected and when crystallised from chloroform–methanol gave the diosphenol (0·14 g.), m. p. 318—320°. The filtrate was evaporated to dryness and the distillate mixed with saturated aqueous dimedone (20 c.c.); after 1 hr. the mixture was concentrated, whereupon the formaldehyde derivative (50 mg.), m. p. and mixed m. p. 189—190°, was obtained.

(iii) 18-*iso*Arjunolic lactone (0·5 g.) in acetic acid (25 c.c.) was treated with chromic oxide (0·27 g.) and kept at room temperature overnight. The solution was then heated to 100° for ½ hr. and poured into water, and the solid was collected. When crystallised first from a large volume of ethanol and then chloroform–methanol it afforded the diosphenol (90 mg.) as leaflets, m. p. 318—320° (decomp.).

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Oxidations with Lead Tetra-acetate. Part II. The Oxidation of Primary Aromatic Amines.*

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Some monosubstituted anilines and α- and β-naphthylamine have been oxidised by lead tetra-acetate in acetic acid.

THE oxidation of primary aromatic amines with phenyl iodosoacetate in benzene (Pausacker, *J.*, 1953, 1989) and in acetic acid (Barlin, Pausacker, and Riggs, *J.*, 1954, 3122) has recently been investigated. The present paper reports a study of the action of lead tetra-acetate in acetic acid.

In preliminary experiments, the amine (*ca.* 1·5—2 × 10^{-4} mole) and lead tetra-acetate (*ca.* 1·5 × 10^{-3} mole) were dissolved in glacial acetic acid (25 ml.), and 1-ml. portions were withdrawn daily and titrated with standardised 0·02N-sodium thiosulphate, after the addition of acidified potassium iodide. An allowance was made for the slight decomposition recorded in a blank experiment. It was also found that intense colours

* "The Oxidation of Glycols with Lead Tetra-acetate," *J.*, 1953, 102, is considered to be Part I.

were produced immediately a solution of lead tetra-acetate (5%; 2 ml.) was added to the amine (*ca.* 2 mg.). The results are shown in Table 1.

TABLE 1.

Subst. in aniline	—	*o*-Me	*m*-Me	*p*-Me	*o*-Cl	*m*-Cl	*p*-Cl	*o*-OMe
$Pb(OAc)_4$ consumed, mols.	4·40	4·47	3·83	3·02	4·07	1·86	3·22	5·58
Immediate colour	violet	violet	violet	violet	brown	red-violet	red-violet	brown

Subst. in aniline	*p*-OMe	*p*-OEt	*o*-NO_2	*m*-NO_2	*p*-NO_2	α-$C_{10}H_7{\cdot}NH_2$	β-$C_{10}H_7{\cdot}NH_2$
$Pb(OAc)_4$ consumed, mols.	3·60	3·71	1·46	2·00	1·50	4·50	3·04
Immediate colour	violet	red-violet	orange	red-brown	orange	deep-red	deep-red

The initial consumption of lead tetra-acetate was rapid and usually followed by a slow reaction during several days. The molar uptake was, in general, greater than that of phenyl iodosoacetate in either benzene or acetic acid.

In most cases the corresponding azo-compound was formed either alone or with other products. The percentage yields of azo-compounds are shown in parentheses—the second and third figures indicating the yields when phenyl iodosoacetate was used in benzene and in acetic acid, respectively: aniline (5, 95, 0); *o*-toluidine (23, 42, 0); *m*-toluidine (18, 56, 0); *p*-toluidine (4, 6, 0); *o*-chloroaniline (56, 39, 25); *m*-chloroaniline (39, 66, 34); *p*-chloroaniline (35, 55, 24); *o*-anisidine (10, 3, 1); *p*-anisidine (16, 5, 4); *o*-nitroaniline (15, 0, 71); *m*-nitroaniline (40, 65, 61); *p*-nitroaniline (43, 53, 63); α-naphthylamine (0, 3, 0); β-naphthylamine (0, 0, 0); and *p*-phenetidine (26, 7, –).

It can be seen that the three different methods give widely different yields of azo-compound; however, those amines containing electron-attracting groups tend to give relatively higher yields.

It is assumed that the reaction mechanism is analogous to that already proposed (Pausacker, *loc. cit.*) for phenyl iodosoacetate :

$$2Pb(OAc)_4 + 2Ar{\cdot}NH_2 \rightleftharpoons 2Pb(OAc)_3{\cdot}NHAr + 2AcOH \rightleftharpoons 2Ar{\cdot}NH\cdot + 2Pb(OAc)_3\cdot$$

$$\downarrow$$

$$2Pb(OAc)_2 + 2AcOH + ArN{:}NAr \longleftarrow ArNH{\cdot}NHAr + 2Pb(OAc)_3$$

This is partially confirmed since hydrazobenzene is oxidised to azobenzene in 95% yield by lead tetra-acetate in acetic acid. As azobenzene is isolated in only 5% yield from the oxidation of aniline, the intermediate PhNH· radical must enter into side-reactions.

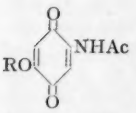
Although benzofurazan oxide was the sole product from the oxidation of *o*-nitroaniline with phenyl iodosoacetate in benzene, it has been found that only 2 : 2′-dinitroazobenzene (15% yield) could be obtained in the present work. This is in accord with the results obtained by using phenyl iodosoacetate in acetic acid, and the explanation is probably that to be given by us elsewhere (*J.*, 1954, in the press). The action on *o*-nitroaniline of lead tetra-acetate in benzene was also studied; the only product isolated was again 2 : 2′-dinitroazobenzene (57% yield). Apparently the formation of the *aci*-nitro-form of *o*-nitroaniline has been repressed (*idem, loc. cit.*) owing to the more polar nature of lead tetra-acetate than of phenyl iodosoacetate.

As stated above, the corresponding azo-compounds were formed during the oxidation of *p*-anisidine and *p*-phenetidine in yields of 16% and 26%, respectively. In addition, compounds *A*, $C_9H_9O_4N$, m. p. 194° (80% yield), and *B*, $C_{10}H_{11}O_4N$, m. p. 216° (59% yield), were also isolated.

Compound *A* contained one acetoxyl and one methoxyl group. It gave a yellow solution in sulphuric acid, but a deep crimson colour with sodium hydroxide solution; this was discharged by addition of zinc dust. After removal of the zinc, a faint pink colour slowly appeared. This suggests a quinonoid structure. During alkaline hydrolysis of compound *A*, 0·97 mole of ammonia was evolved.

Barlin and Riggs (*J.*, 1954, 3125) report the formation (in trace amounts) of a compound, m. p. 216°, from the oxidation of phenacetin with phenyl iodosoacetate in acetic acid. The m. p. of compound *B* is undepressed on admixture with a sample kindly supplied by Dr. Riggs.

On the basis of the above evidence, structure (I) appears most likely for compounds *A* and *B*.



(I; *A*, R = Me; *B*, R = Et)

Dr. Riggs informs us that the ultra-violet absorption spectrum of compound *B* is consistent with the proposed structure (cf. Braude, *J.*, 1945, 490).

The sole product isolated from the oxidation of α-naphthylamine was 1 : 4-naphthaquinone in 16% yield. Oxidation with phenyl iodosoacetate in benzene solution (Pausacker, *loc. cit.*) gave only a low yield (3%) of 1 : 1′-azonaphthalene.

1 : 2-6 : 7-Dibenzophenazine (3% yield), 2-amino-1 : 4-naphthaquinone (25% yield), and 2-acetamido-1 : 4-naphthaquinone 1-β-naphthylamine anil (60% yield) were isolated from the oxidation of β-naphthylamine. 1 : 2-6 : 7-Dibenzophenazine (29%) and an unidentified high-melting substance (66%) were formed by oxidation of β-naphthylamine by phenyl iodosoacetate in benzene (*idem, loc. cit.*), and with phenyl iodosoacetate in acetic acid (Barlin, Pausacker, and Riggs, *loc. cit.*) 2-acetamido-1 : 4-naphthaquinone (34%), 2-acetamido-1 : 4-naphthaquinone 1-β-naphthylamine anil (25%), and an unidentified high-melting substance (14%) are formed.

Thus, although phenyl iodosoacetate and lead tetra-acetate are generally regarded as being oxidising agents of the same type, they may effect widely different oxidations with aromatic amines. It is also apparent that their mode of action is conditioned by the solvent used (cf. Barron, Cavill, Cole, Gilham, and Solomon, *Chem. and Ind.*, 1954, 76).

Experimental

All melting points are corrected. Analyses are by Dr. W. Zimmermann.

Method.—The amine (*ca.* 1—2 g.) and an acetic acid solution of the amount of lead tetra-acetate indicated in Table 1 were set aside at room temperature until reaction was complete. The solvent was removed under reduced pressure and the residue extracted with hot benzene. The cooled benzene extract was filtered, concentrated to *ca.* 50 ml., and chromatographed on alumina, benzene being used as eluant. Azo-compounds were in the bottom band and were identified by m. p. and mixed-m. p. determinations. The results are in Table 2.

Products.—The products of the oxidations are :

Hydrazobenzene yielded azobenzene (95%), m. p. and mixed m. p. 68°.

p-Anisidine (4·03 g.) yielded (*a*) 4 : 4′-dimethoxyazobenzene (0·632 g.), m. p. and mixed m. p. 163° (from methanol), and (*b*) *compound* A (3·21 g.), orange needles (from ethanol), m. p.

Table 2.

Substituents in azobenzene	—	2 : 2′-Me_2	3 : 3′-Me_2	4 : 4′-Me_2	2 : 2′-Cl_2	3 : 3′-Cl_2
M. p., found	68°	53	54	143	135	101
M. p., lit.	68°	55	55	143	137	101

Substituents in azobenzene	4 : 4′-Cl_2	2 : 2′-$(OMe)_2$	2 : 2′-$(NO_2)_2$	3 : 3′-$(NO_2)_2$	4 : 4′-$(NO_2)_2$
M. p., found	184	153	210	152	221
M. p., lit.	184	153	210	153	220

194° (Found : C, 55·6, 55·4; H, 4·7, 4·6; N, 7·3; OMe, 15·9; Ac, 21·6%; *M*, 211, 224. $C_9H_9O_4N$ requires C, 55·4; H, 4·6; N, 7·2; 1OMe, 15·9; 1Ac, 22·0%; *M*, 195).

Hydrolysis of compound *A* with sodium hydroxide (20%) gave an alkaline gas which was distilled into standard acid. Back-titration of the excess of acid indicated that 0·97 mole of base had been formed. An aqueous solution of the base showed with ferric sulphate a negative test for hydroxylamine (cf. Meyeringh, *Ber.*, 1877, **10**, 1940), but gave a positive test for ammonia with Nessler's reagent.

p-Phenetidine (1·93 g.) yielded (*a*) 4 : 4′-diethoxyazobenzene (0·502 g.), m. p. and mixed m. p. 160° (from ethanol), and (*b*) *compound* B (1·15 g.), which crystallised from ethanol as mustard-coloured needles, m. p. 216° (Found : C, 57·2, 57·5; H, 5·2, 5·4; N, 6·8; OEt, 17·2. $C_{10}H_{11}O_4N$ requires C, 57·4; H, 5·3; N, 6·7; 1OEt, 21·5%).

α-Naphthylamine yielded 1 : 4-naphthaquinone (16%) which, after vacuum-sublimation at 100° and crystallisation from light petroleum (b. p. 90—110°), had m. p. and mixed m. p. 124° (sealed tube). This gave a characteristic red-brown solution in sodium hydroxide.

β-Naphthylamine (6·00 g.) yielded (*a*) 1 : 2-6 : 7-dibenzophenazine (0·169 g.), m. p. and

mixed m. p. 283° (from benzene); (*b*) 2-acetamido-1 : 4-naphthaquinone 1-β-naphthylamine anil (3·62 g.), which crystallised from benzene or ethanol as red plates or purple needles, m. p. 209° (Found: C, 77·3, 77·5; H, 4·7, 4·7; Ac, 11·7. Calc. for $C_{22}H_{16}O_2N_2$: C, 77·6; H, 4·7; 1Ac, 12·6%) [the latter compound had properties identical with that obtained from the oxidation of β-naphthylamine with phenyl iodosoacetate in acetic acid (Barlin, Pausacker, and Riggs, *loc. cit.*) and a mixture of the two specimens showed no depression of m. p.]; and (*c*) 2-amino-1 : 4-naphthaquinone (1·48 g.), which had m. p. and mixed m. p. 207° (from benzene or ethanol) (Found: C, 69·8; H, 4·2; N, 8·35. Calc. for $C_{10}H_7O_2N$: C, 69·5; H, 4·05; N, 8·1%).

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Researches on Polyenes. Part II. The Synthesis of Cosmene.*

By P. NAYLER and M. C. WHITING.

[Reprint Order No. 5536.]

The structure, 2 : 6-dimethylocta-1 : 3 : 5 : 7-tetraene, (I), assigned to the dehydromonoterpene, "cosmene," is confirmed by total synthesis. Spectroscopic data for some natural and synthetic tetraenes are discussed, and deductions are made about their steric structures.

A HYDROCARBON, $C_{10}H_{14}$, named cosmene, was recently isolated by Sörensen and Sörensen (*Acta Chem. Scand.*, 1954, **8**, 284) from *Cosmos bipinnatus* Cav., and identified spectroscopically in eight other species (of seven different genera) of the family Compositae. On the basis of its ultra-violet and infra-red spectra, and of biogenetic considerations, the structure (I), with a *trans*-configuration at the $-CH{=}CH-$ grouping, was proposed; it would thus be the first dehydroterpene, and incidentally the first acyclic terpenoid with an *iso*-propenyl grouping known to occur in nature (cf. *inter al.*, Barnard, Bateman, Harding, Koch, Sheppard, and Sutherland, *J.*, 1950, 915).

Bates, Jones, Nayler, and Whiting (unpublished work) have observed the reduction of 1 : 4-diphenylbut-2-yne-1 : 4-diol to 1 : 4-diphenylbuta-1 : 3-diene in fair yield by lithium aluminium hydride. This reaction is synthetically equivalent to semihydrogenation followed by the action of phosphorus di-iodide (Kuhn and Wallenfels, *Ber.*, 1938, **71**, 1889); if general, it should make possible a very simple synthesis of (I):

$$H_2C{=}CMe{\cdot}CHO + BrMg{\cdot}C{\equiv}C{\cdot}CMe(O{\cdot}MgBr){\cdot}CH{=}CH_2 \longrightarrow$$

$$H_2C{=}CMe{\cdot}CH(OH){\cdot}C{\equiv}C{\cdot}CMe(OH){\cdot}CH{=}CH_2 \xrightarrow{LiAlH_4} H_2C{=}CMe{\cdot}CH{=}CH{\cdot}CH{=}CMe{\cdot}CH{=}CH_2$$

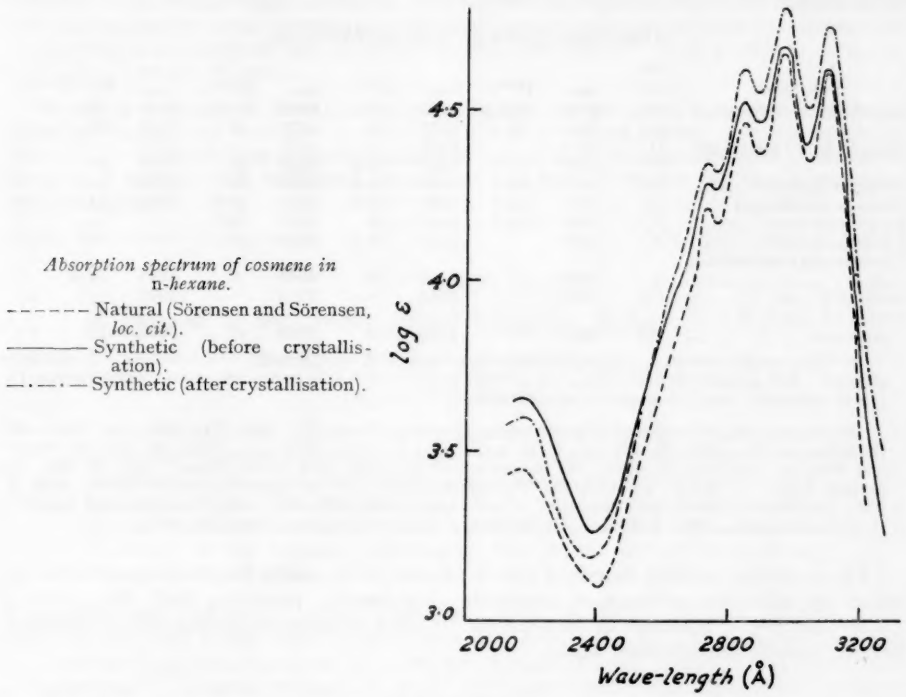
(II) (I)

3-Methylpent-1-en-4-yn-3-ol (Cymerman, Heilbron, and Jones, *J.*, 1945, 90; Oroshnik and Mebane, *J. Amer. Chem. Soc.*, 1949, **71**, 2062) was condensed with α-methylacraldehyde *via* the bisbromomagnesium derivative, giving the desired glycol (II) in 72% yield. This was treated with lithium aluminium hydride (4 mols.) in ether at 34°, whereby, in addition to hydroxylic by-products which were not investigated, a fragrant hydrocarbon, $C_{10}H_{14}$, was obtained in 35% yield. Final purification by recrystallisation at −70° gave a product with m. p. −1° to 0°, agreeing well with the melting point (−2° to −1°) of cosmene. The infra-red spectra of the synthetic hydrocarbon, before and after recrystallisation, scarcely differed, and were identical, as far as could be ascertained, with the spectrum of cosmene determined by Professor Sörensen. A bis-maleic anhydride adduct, m. p. 198°, identical with that of cosmene, was obtained readily.

Slight differences in the ultra-violet spectra of the synthetic hydrocarbon before and after recrystallisation are illustrated in the Figure; the data for the natural hydrocarbon, which had also been recrystallised repeatedly, actually agree better with the former. There is no doubt that the increase in intensity of absorption following recrystallisation is real, since values of 61,200 and 62,500 were obtained in duplicate experiments starting with

* Part I, *J.*, 1954, 3217.

material with ε 49,500 (values refer to the 2965-Å band). It therefore seems likely that the (analytically pure) hydrocarbon obtained by reduction was nevertheless a mixture of stereoisomers about the trisubstituted ethylenic linkage. The two isomers of (I) with a *cis*-ethylenic linkage would have absorbed intensely in the infra-red below 750 cm.$^{-1}$ and therefore cannot have been present in quantity. Since identical maleic anhydride adducts were obtained, the natural hydrocarbon and the recrystallised synthetic hydrocarbon must have been the same isomer, almost certainly that with an all-*trans*-system of ethylenic bonds (cf. Craig, *J. Amer. Chem. Soc.*, 1950, **72**, 1678). The lower intensity of absorption observed for the natural hydrocarbon may have been the result of an impurity, *e.g.*, ocimene, more difficult to separate by crystallisation than the mono-*cis*-stereoisomer of (I). More



probably it was merely a consequence of the great experimental difficulty of working with easily polymerised liquids on a small scale.

The ultra-violet absorption spectra of cosmene and a number of other conjugated tetraenes are summarised in the Table; several conclusions may be drawn. In all cases marked fine-structure is present, the interval between bands being constant at *ca.* 1450 cm.$^{-1}$, provided that Blout and Fields's data for deca-2 : 4 : 6 : 8-tetraene (which we have confirmed) are accepted in preference to Kuhn and Grundmann's older values (*Ber.*, 1938, **71**, 446). The bathochromic effect of substituent methyl groups is about +30 Å each compared with about +45 Å in dienes, and appears to be independent of their location on the tetraene system, as has often been assumed. The considerable discrepancy between "isomerised arachnidonic acid," *i.e.*, an octadecatetraenoic acid of unknown structure, probably all-*trans*, and β-parinaric acid (Ahlers, Brett, and McTaggart, *J. Appl. Chem.*, 1953, **3**, 433), *i.e.*, all-*trans*-octadeca-9 : 11 : 13 : 15-tetraenoic acid, on the one hand, and (all-*trans*-)deca-2 : 4 : 6 : 8-tetraene, on the other, points to a larger "weight effect" [$\Delta\lambda(C_6H_{13}$, approx.) − $\Delta\lambda(CH_3) = 20$—25 Å] on the absorption spectra of conjugated tetraenes than is encountered with dienes (cf. Bates, Jones, and Whiting, *J.*, 1954, 1854).

When a *cis*-linkage is introduced, as in α-parinaric acid, the intensity of adsorption is reduced, and the maxima are displaced to *longer* wave-lengths. These effects are analogous to those observed in 1 : 4-disubstituted dienes (Nichols, Herb, and Riemenschneider, *J. Amer. Chem. Soc.*, 1951, **73**, 247) and in the hexa-2 : 4-dienoic acids (Allan, Jones, and Whiting, unpublished work). Zechmeister's rule (*Experientia*, 1954, **10**, 1), that an all-*trans*-polyene absorbs maximally at longer wave-lengths than any of its stereoisomers, is thus untrue for simple *unbranched* polyenes; though his generalisation that the all-*trans* compound shows the highest extinction coefficient does hold within this group.

From the Table it is clear that the Centaur Y compounds of Hellström and Löfgren (*Acta Chem. Scand.*, 1952, **6**, 1024) must be tri- or tetra-substituted tetraenes or, more probably, possess one or more *cis*-linkages.

*Absorption spectra of conjugated tetraenes.**

Substance	Solvent †	$\lambda_{max.}$	$10^{-3}\varepsilon$	$\lambda_{max.}$	$10^{-3}\varepsilon$	$\lambda_{max.}$	$10^{-3}\varepsilon$	$\lambda_{max.}$	$10^{-3}\varepsilon$	Ref.
Octa-1 : 3 : 5 : 7-tetraene	CH	3040	(9*x*) ‡	2905	(10*x*)	2780	(8*x*)	2680	(6*x*)	1
	H	3200	56	2970	56	2830	33	2720	20	2
Deca-2 : 4 : 6 : 8-tetraene	H	3100	—	2950	—	2830	—	2720	—	3
	H	3100	76·5	2960	84·5	2830	51	2730	25	4
Cosmene (natural)	H	3097	42·7	2960	47·5	2830	30	2720	16·9	5
Cosmene (synthetic)	H	3105	55·5	2965	62·5	2845	41·6	2740	21·8	6
α-Parinaric acid	A	3200	61·7	3050	66	2915	42·7	—	—	7
β-Parinaric acid	A?	3160	—	3010	73·5	2880	—	—	—	8
"Isomerised arachnidonic acid"	A	3150	67	3000	73	2860	58	2715	21·3	9
Centaur Y_1 and Y_2	CH	3195	—	3045	—	2915	—	2800	—	10
Deca-1 : 3 : 5 : 7 : 9-pentaene	IO	3343	118	3180	112	3039	63	2908	25	11

* Wave-lengths are in Å. † H, hexane or heptane : CH, *cyclo*hexane; IO, *iso*octane : A, absolute ethanol. For polyene hydrocarbons the solvent shifts within this group are small; see reference 11. ‡ *x* is unknown; intensities quoted are relative.

References: (1) Woods and Schwartzman, *J. Amer. Chem. Soc.*, 1949, **71**, 1396; (2) Kuhn and Grundmann, *Ber.*, 1938, **71**, 446; (3) Blout and Fields, *J. Amer. Chem. Soc.*, 1948, **70**, 189; (4) Nayler and Whiting, unpublished work; (5) Sörensen and Sörensen, *Acta Chem. Scand.*, 1954, **8**, 284; (6) present work; (7) Riley, *J.*, 1950, **14**; (8) Ahlers, Brett, and McTaggart, *J. Appl. Chem.*, 1953, **3**, 433; (9) Mowry, Brode, and Brown, *J. Biol. Chem.*, 1942, **142**, 671; (10) Hellström and Löfgren, *Acta Chem. Scand.*, 1952, **6**, 1024; (11) Mebane, *J. Amer. Chem. Soc.*, 1952, **74**, 5527.

The synthetic method described above appears to be easily the most convenient yet found for aliphatic polyenes of moderate chain-length, providing that the grouping >CH=CH·CH=C< is present in the molecule. It is not, however, applicable to 2 : 5-dimethylhexa-2 : 4-diene (unpublished work).

Experimental

2 : 6-*Dimethylocta*-1 : 7-*dien*-4-*yne*-3 : 6-*diol*.—A solution of ethylmagnesium bromide was prepared from magnesium (2·5 g.) in ether under nitrogen, and ether was replaced by benzene until the b. p. of the distillate reached 70° (final volume 150 c.c.). The mixture was cooled to 0° while a solution of 3-methylpent-1-en-4-yn-3-ol (Oroshnik and Mebane, *loc. cit.*) (1·4 g.) in ether (10 c.c.) was added; stirring was continued for 3 hr. at room temperature. After the mixture had been cooled to 0°, α-methylacraldehyde (3·5 g.) in benzene (25 c.c.) was added, and the mixture was stirred for 5 hr. at room temperature; the originally insoluble viscous complex then dissolved. Addition of ammonium chloride solution, isolation of the neutral fraction, and distillation gave the *glycol* (5·7 g.), b. p. 75—80° (bath-temp.)/10^{-3} mm., n_D^{16} 1·4946 (Found: C, 72·05; H, 8·65. $C_{10}H_{14}O_2$ requires C, 72·25; H, 8·5%).

2 : 6-*Dimethylocta*-1 : 3 : 5 : 7-*tetraene* (*Cosmene*).—The glycol (3·0 g.) in ether (50 c.c.) was added to a solution of lithium aluminium hydride (2·5 g.) in ether (200 c.c.), and the mixture was heated under reflux for 4 hr. Cautious addition of ice and aqueous tartaric acid, and ether-extraction gave a solution which was dried ($MgSO_4$) at −4° under nitrogen. Removal of ether at 0° gave a residue which was extracted with light petroleum (b. p. 40–60°; 5 × 30 c.c.) at 20° and passed through activated alumina. Solvent was again removed at 0°, and the residue was distilled, giving the *tetraene* (0·9 g.), b. p. 50° (bath-temp.)/0·2 mm., n_D^{18} 1·5852, m. p. −7°

to −5° (Found: C, 89·3; H, 10·7. $C_{10}H_{14}$ requires C, 89·5; H, 10·5%). Four recrystallisations from pentane at −70° raised the m. p. to −1° to 0°, and the intensity of absorption as illustrated; the refractive index was almost unchanged, n_D^{18} now 1·5850. Sörensen and Sörensen (*loc. cit.*) give b. p. 30°/0·3 mm., n_D^{20} 1·584, m. p. −2° to −1°. The synthetic hydrocarbon polymerised and oxidised rapidly in air, but could be stored for several months at −60° in nitrogen.

5 : 6′-Dimethyl-1 : 2 : 3 : 4 : 1′ : 2′ : 3′ : 4′-octahydrodiphenyl-2 : 3 : 2′ : 3′-tetracarboxylic Dianhydride.—A solution of maleic anhydride (0·65 g.) in benzene (10 c.c.) was cooled until mainly solid, and the tetraene (0·3 g.) was added, whereupon a yellow colour developed at once. The mixture was warmed to room temperature, then set aside at 0° for 3 days. Evaporation of the benzene and extraction with light petroleum (b. p. 60—80°) left a residue which was crystallised repeatedly from benzene–light petroleum, then acetone–light petroleum, giving needles, m. p. 198°, undepressed on admixture with a specimen of the maleic anhydride adduct of cosmene, for which Sörensen and Sörensen (*loc. cit.*) give m. p. 198—199° (Found: C, 65·3; H, 5·5. Calc. for $C_{18}H_{18}O_6$: C, 65·45; H, 5·5%).

We thank Professor N. A. Sörensen for his interest and the gift of a sample of the maleic anhydride adduct, and Professor E. R. H. Jones, F.R.S., for his interest and helpful advice. One of us (P. N.) is indebted to the Department of Scientific and Industrial Research. We thank Messrs. E. S. Morton and H. Swift for microanalyses, and Miss W. Peadon and Miss J. Shallcross for infra-red data.

THE UNIVERSITY, MANCHESTER. [*Received, July 8th*, 1954.]

A Descent of the Sugar Series based on Ketose Mercaptols.

By E. J. BOURNE and R. STEPHENS.

[Reprint Order No. 5582.]

The diethyl and dibenzyl mercaptols of penta-*O*-acetyl-*keto*-D-fructose have been prepared and converted into the corresponding disulphones with monoperphthalic acid. With methanolic ammonia, the disulphones yield the D-erythrose bisacetamide derivative and a tetra-alkylsulphonylpropane. The mechanism of this reaction is discussed, and a comment is made on the structures of the supposed unsaturated disulphones derived from aldose mercaptals by oxidation.

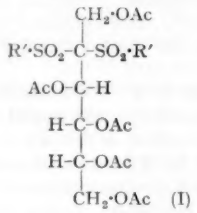
MACDONALD and FISCHER (*J. Amer. Chem. Soc.*, 1952, **74**, 2087; *Biochim. Biophys. Acta*, 1953, **12**, 203) and Hough and Taylor (*Chem. and Ind.*, 1954, 575) have shown that the unsaturated disulphones produced by oxidation of unsubstituted aldose diethyl mercaptals are hydrolysed by aqueous ammonia to diethylsulphonylmethane and the next lower aldose. The reaction is analogous to that described by Rothstein (*J.*, 1934, 684; 1940, 1560) for simpler compounds, thus:

$$R{\cdot}CH{:}C(SO_2{\cdot}Et)_2 + HX \longrightarrow R{\cdot}CHX{\cdot}CH(SO_2{\cdot}Et)_2 \xrightarrow{(X = OH)} R{\cdot}CHO + CH_2(SO_2{\cdot}Et)_2$$

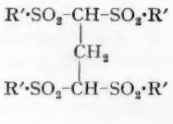
We now report a similar cleavage with ammonia of disulphones derived from penta-*O*-acetylfructose dialkyl mercaptols, but in these cases two carbon atoms are removed from the sugar chain. This degradation should be useful in the characterisation of new ketoses.

Penta-*O*-acetyl-*keto*-D-fructose (Hudson and Brauns, *J. Amer. Chem. Soc.*, 1915, **37**, 2736) was converted into the diethyl mercaptol, from which D-*fructo*-1 : 3 : 4 : 5 : 6-penta-acetoxy-2 : 2-diethylsulphonylhexane (I; R′ = Et) was produced by oxidation with monoperphthalic acid in ether (cf. MacDonald and Fischer, *loc. cit.*, 1952). The presence of sulphone groups was confirmed by the infra-red absorption spectrum, which showed peaks at 1333, 1319, 1305, and 1150 cm.$^{-1}$, in good agreement with the values 1336—1312 and 1164—1130 cm.$^{-1}$ assigned to these groups by Barnard, Fabian, and Koch (*J.*, 1949, 2442). In dry pyridine the disulphone gave a colourless solution, in contrast to the cherry-red solutions reported for unsaturated disulphones of the supposed type $R{\cdot}CH{:}C(SO_2{\cdot}R')_2$ (MacDonald and Fischer, *loc. cit.*, 1952). Moreover, the ultra-violet absorption spectrum

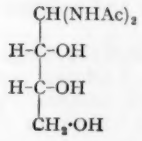
of an ethanolic solution of the disulphone corresponded to the " saturated type " illustrated by these authors.



(I)



(II)

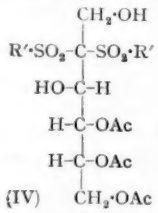


(III)

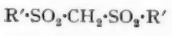
Treatment of the disulphone (I; R′ = Et) with ammonia in methanol at room temperature for 2 days effected partial deacetylation and cleavage of the main carbon chain. Two crystalline fragments were isolated, namely, 1 : 1 : 3 : 3-tetraethylsulphonylpropane (II; R′ = Et) and the D-erythrose bisacetamide derivative (III). The latter was characterised by its consumption of 2·1 mols. of lead tetra-acetate, by conversion into its triacetate, and by comparison of its infra-red absorption spectrum with that of the L-erythrose analogue, prepared by Wohl's method (*Ber.*, 1899, **32**, 3666) from L-arabinose.

In analogous reactions, penta-*O*-acetyl-*keto*-D-fructose was converted, *via* the dibenzyl mercaptol and the disulphone (I; R′ = C_6H_5·CH_2), into the bisacetamide (III); in this case, however, the disulphone was not purified. An attempt to isolate the other fragment (II; R′ = C_6H_5·CH_2) produced by ammonolysis gave only a syrup, which slowly decomposed to a deep red tar.

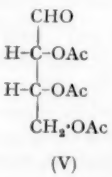
The profound changes occurring during ammonolysis of the disulphones (I) can be explained readily in terms of well-established reactions. Electron-attracting centres are known to increase the rate of the usual bimolecular basic hydrolysis (with acyl–oxygen fission) of neighbouring ester groups (cf. Ingold, " Structure and Mechanism in Organic Chemistry," G. Bell and Sons, Ltd., London 1953, pp. 754—760; see also Henne and Pelley, *J. Amer. Chem. Soc.*, 1952, **74**, 1426), and so it is reasonable to suppose that the 1- and 3-acetoxy-groups would be more labile in ammonia than the others, and that a D-*fructo*-4 : 5 : 6-triacetoxy-1 : 3-dihydroxy-2 : 2-dialkylsulphonylhexane (IV) would be produced during the early stages of the reaction.



(IV)



(VI)



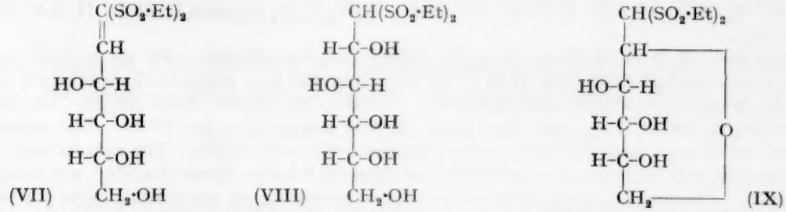
(V)

From Rothstein's observations (*loc. cit.*), (IV) would be expected to yield, in two stages, 2 : 3 : 4-tri-*O*-acetyl-*aldehydo*-D-erythrose (V), formaldehyde, and a dialkylsulphonylmethane (VI). In this part of the reaction, the role of (VI) can be likened to that of HCN in the reversal of cyanohydrin formation. Further action of the ammonia on (V) would entail acetyl migration and partial deacetylation to the D-erythrose bisacetamide derivative. There would of course be a certain amount of overlapping of the above steps in the reaction, giving rise to other intermediates; the main outline of the mechanism advanced is in keeping with current theories that bisacetamido-sugars arise, not from acetamide, but by an intramolecular acyl migration from oxygen to nitrogen (Isbell and Frush, *J. Amer. Chem. Soc.*, 1949, **71**, 1579; Deulofeu and Deferrari, *J. Org. Chem.*, 1952, **17**, 1087).

It is known that formaldehyde and diethylsulphonylmethane in the presence of a basic catalyst give 1 : 1 : 3 : 3-tetraethylsulphonylpropane (Kötz, *Ber.*, 1900, **33**, 1120); indeed, we employed this reaction to prepare a reference sample of the latter compound. Since these two precursors were expected to arise during ammonolysis (see above), the origin of

the tetrasulphone (II) is clear. Of several aldehydes examined by Kötz, formaldehyde was the only one which condensed with disulphones in this way, and so it is unlikely that 2 : 3 : 4-tri-*O*-acetyl-*aldehydo*-D-erythrose would undergo a similar reaction.

Interesting comparisons can be made between the acetylated fructose-derived disulphones and those produced from aldoses, which in every case except one (that of the mannose-derived material which appears to be an uncharacterised mixture) have been assigned



a structure of type (VII), rather than (VIII); the products from acetylated aldose mercaptals have been represented as the corresponding unsaturated acetates (MacDonald and Fischer, *locc. cit.*; Hough and Taylor, *loc. cit.*). Presumably, the saturated disulphone (VIII) is formed first and then loses the elements of water (or of acetic acid in the case of an acetate). A fructose-derived disulphone cannot become unsaturated in this way, because it does not carry an acidic hydrogen on the same carbon atom as the two sulphone groups.

The action of ammonia on disulphones derived from aldoses is interesting. The disulphones from xylose, arabinose, and 3-deoxyglucose diethyl mercaptals [designated as of type (VII)] yield diethylsulphonylmethane and the next lower aldose, whereas the glucose-derived tetra-acetate of (VII) adds ammonia across the double bond to give a 2-acetamido-2-deoxy-derivative (MacDonald and Fischer, *locc. cit.*; Hough and Taylor, *loc. cit.*). It may well be that in all these cases the 2-amino-2-deoxy-compound and the 2-hydroxy-compound are the first products, and that these then disproportionate in the manner shown by Rothstein (*loc. cit.*) for simpler compounds, unless acyl migration can occur to stabilise the amino-group as its *N*-acetyl derivative. There is another possibility, which has a bearing on our observation (to be reported in detail later) that treatment of D-*arabo*-3 : 4 : 5 : 6-tetra-acetoxy-1 : 1-diethylsulphonylhex-1-ene with sodium methoxide in methanol gives a methoxy-compound; this is that unsubstituted compounds of type (VII), but not their acetates, may exist, under suitable conditions, in equilibrium with the cyclic form (IX).

Note Added in Proof.—Other evidence that the diethylsulphonyl derivatives of D-galactose, D-glucose, and D-mannose are cyclic has now been provided by Hough and Taylor (*Chem. and Ind.*, 1954, 1018).

Experimental

1 : 3 : 4 : 5 : 6-*Penta*-O-*acetyl*-keto-D-*fructose*.—Tetra-*O*-acetyl-D-fructose {39%; m. p. 127—129°; $[\alpha]_D^{15}$ −80·5° (*c*, 5·3 in $CHCl_3$)} was prepared by partial acetylation of D-fructose, as described by Hudson and Brauns (*loc. cit.*) (Found: C, 48·6; H, 6·0; Ac, 50·3. Calc. for $C_{14}H_{20}O_{10}$: C, 48·3; H, 5·8; Ac, 49·4%); Tollens ("Kurzes Handbuch der Kohlenhydrate," Barth, Leipzig, 1934, p. 373) gave m. p. 130—132° and $[\alpha]_D$ −92° (in $CHCl_3$). Further acetylation of this compound by Hudson and Brauns's method yielded 1 : 3 : 4 : 5 : 6-penta-*O*-acetyl-*keto*-D-fructose (25% based on fructose), m. p. 65—68°, $[\alpha]_D^{16}$ +13·0° (*c*, 6·1 in $CHCl_3$) (Found: C, 49·5; H, 5·8; Ac, 56·7. Calc. for $C_{16}H_{22}O_{11}$: C, 49·2; H, 5·7; Ac, 55·1%); Hudson and Brauns (*loc. cit.*) reported m. p. 70° and $[\alpha]_D^{20}$ +34·4° (in $CHCl_3$). The ultra-violet absorption spectrum of an ethanolic solution showed a peak at 280 mμ ($\log_{10}\varepsilon$ 1·5), in agreement with the results of Bredereck, Höschele, and Huber (*Ber.*, 1953, **86**, 1271).

1 : 3 : 4 : 5 : 6-*Penta*-O-*acetyl*-keto-D-*fructose Diethyl Mercaptol*.—The above penta-acetate was treated with ethanethiol according to Wolfrom and Thompson's method (*J. Amer. Chem. Soc.*, 1934, **56**, 880), and the product was crystallised from ether–light petroleum (b. p. 60—80°) and then from absolute ethanol, to give the mercaptol (25%), m. p. 80—81°, $[\alpha]_D^{16}$ +20·0° (*c*, 1·5 in $CHCl_3$) (Found: C, 48·0; H, 6·3; S, 13·2; Ac, 43·0. Calc. for $C_{20}H_{32}O_{10}S_2$: C, 48·4;

H, 6·5; S, 12·9; Ac, 43·3%). Wolfrom and Thompson (*loc. cit.*) gave m. p. 83°, $[\alpha]_D^{27}$ +20·0° (in $CHCl_3$).

1 : 3 : 4 : 5 : 6-*Penta*-O-*acetyl*-keto-D-*fructose Dibenzyl Mercaptol*.—1 : 3 : 4 : 5 : 6-Penta-*O*-acetyl-*keto*-D-fructose (16·0 g.) was condensed with toluene-ω-thiol (20 c.c.), by Wolfrom and Thompson's method (*loc. cit.*) except that, after the initial mixing at −10°, the temperature was maintained at *ca.* 25° for 24 hr. Repeated crystallisation of the product from absolute ethanol afforded the *dibenzyl mercaptol* (4·40 g.), m. p. 110—111°, $[\alpha]_D^{12}$ +40·1° (*c*, 5·0 in $CHCl_3$) (Found : C, 58·3; H, 5·7; S, 10·7; Ac, 37·4. $C_{30}H_{36}O_{10}S_2$ requires C, 58·1; H, 5·8; S, 10·3; Ac, 34·7%).

D-fructo-1 : 3 : 4 : 5 : 6-*Penta-acetoxy*-2 : 2-*diethylsulphonylhexane*.—To an ice-cold solution of the above diethyl mercaptol (0·75 g.) in dry ether (20 c.c.) was added an ethereal solution (30 c.c.) of monoperphthalic acid (4·8 mols.; Böhme, *Org. Synth.*, 1940, **20**, 70); the mixture was cooled in ice for 1 hr. and then kept at room temperature for 40 hr. The solvent was removed at 12 mm. and the residue was extracted with chloroform. The extract was washed with aqueous sodium hydrogen carbonate, and then with water, dried (Na_2SO_4), and evaporated at 12 mm. The residue, crystallised several times from ethanol, gave rectangular plates of the *disulphone* (0·62 g.), m. p. 144—145°, $[\alpha]_D^{17}$ +7·2° (*c*, 2·2 in $CHCl_3$) (Found : C, 43·0; H, 5·7; S, 11·3. $C_{20}H_{32}O_{14}S_2$ requires C, 42·9; H, 5·75; S, 11·4%). A solution of the compound in dry pyridine remained colourless.

Treatment of D-fructo-1 : 3 : 4 : 5 : 6-*Penta-acetoxy*-2 : 2-*diethylsulphonylhexane with Ammonia in Methanol*.—A methanolic solution (200 c.c.) of the hexane derivative (2·09 g.) was saturated with ammonia gas at 0°, kept at room temperature for 48 hr., and evaporated at 12 mm. to a crystalline mass, from which acetamide was removed by sublimation at 60°/0·01 mm. Recrystallisation of the residue from absolute methanol gave the D-erythrose bisacetamide derivative (1 : 1-bisacetamido-1-deoxy-D-erythrose) (0·40 g.), m. p. 210—211° (decomp.), $[\alpha]_D^{19}$ +9·0° (*c*, 1·3 in H_2O) (Found : C, 43·5; H, 7·2; N, 12·3. Calc. for $C_8H_{16}O_5N_2$: C, 43·6; H, 7·3; N, 12·7%). The infra-red absorption spectrum, over the frequency range 1800—650 $cm.^{-1}$, was identical with that of the L-erythrose analogue, m. p. 212° (decomp.), prepared by Wohl's method (*loc. cit.*). Wohl recorded m. p. 210° (decomp.), $[\alpha]_D$ −7·9°.

The mother-liquors subsequently deposited large rectangular plates of 1 : 1 : 3 : 3-tetraethylsuphonylpropane (0·13 g.), m. p. 158—159°, unchanged by recrystallisation from absolute ethanol (Found : C, 32·2; H, 5·9; S, 31·3. Calc. for $C_{11}H_{24}O_8S_4$: C, 32·0; H, 5·9; S, 31·1%). The infra-red absorption spectrum, measured from 1800 to 650 $cm.^{-1}$, was identical with that of an authentic specimen of 1 : 1 : 3 : 3-tetraethylsulphonylpropane (m. p. and mixed m. p. 158—160°), prepared from diethylsulphonylmethane and 40% aqueous formaldehyde in the presence of piperidine (cf. Kötz, *loc. cit.*); the spectra differed from that of diethylsulphonylmethane (m. p. 103°).

Oxidation of the D-*Erythrose Bisacetamide Derivative with Lead Tetra-acetate*.—The bisacetamide derivative (0·0232 g.) was treated with lead tetra-acetate in glacial acetic acid and the extent of the oxidation was determined iodometrically, as described by Hockett and McClenahan (*J. Amer. Chem. Soc.*, 1939, **61**, 1667). The amount of tetra-acetate consumed was 2·0 mols. after 15 hr. and 2·1 mols. after 40 hr.

2 : 3 : 4-*Tri*-O-*acetyl*-D-*erythrose Bisacetamide Derivative*.—The D-erythrose bisacetamide derivative (0·40 g.), treated with acetic anhydride (1·40 c.c.) in pyridine (2·00 c.c.) by Deulofeu's method (*J.*, 1932, 2973), gave a water-soluble acetate, which crystallised from ethanol–ether in needles (0·45 g.), m. p. 148—150°, $[\alpha]_D^{20}$ +23·2° (*c*, 4·5 in $CHCl_3$). The infra-red absorption spectrum, measured between 1800 and 650 $cm.^{-1}$, was identical with that of an authentic specimen of the 2 : 3 : 4-tri-*O*-acetyl-L-erythrose bisacetamide derivative, m. p. 149—150°, $[\alpha]_D^{22}$ −25·0° (*c*, 3·3 in $CHCl_3$).

The D-*Erythrose Bisacetamide Derivative from* 1 : 3 : 4 : 5 : 6-*Penta*-O-*acetyl*-keto-D-*fructose Dibenzyl Mercaptol*.—The dibenzyl mercaptol (4·40 g.) was oxidised with monoperphthalic acid (4·8 mols.) in ether (80 c.c.), as described above. A methanolic solution (200 c.c.) of the product (4·26 g.) was saturated with ammonia gas at 0°; a pale orange colour soon developed. After 48 hr. at room temperature, the crystalline precipitate of the D-erythrose bisacetamide derivative (0·98 g.) was collected; it had m. p. 206—209° (decomp.), not depressed on admixture with the specimen mentioned above. The infra-red absorption spectra (1800—650 $cm.^{-1}$) of the two samples were identical. An attempt to isolate 1 : 1 : 3 : 3-tetrabenzylsulphonylpropane by evaporation of the mother-liquors gave a syrup, which slowly decomposed to a deep red tar.

Infra-red Absorption Spectra.—Infra-red absorption spectra were determined on mulls in "Nujol," with a Grubb–Parsons Single Beam Spectrometer with sodium chloride optics.

The authors are indebted to Professor M. Stacey, F.R.S., for his interest, to Dr. D. H. Whiffen for his advice on the interpretation of the spectra, and to Courtaulds' Scientific and Educational Trust Fund for the award of a scholarship to one of them (R. S.). The expenses were covered by a grant from the Special Research Fund of this University.

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Aluminium Phosphates: Phase-diagram and Ion-exchange Studies of the System Aluminium Oxide–Phosphoric Oxide–Water at 25°.

By R. F. JAMESON and J. E. SALMON.

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Phase-diagram studies in the range from 1% to 60% of phosphoric oxide have shown the following to be the stable solid phases at 25°: $Al_2O_3,P_2O_5,7H_2O$; $Al_2O_3,P_2O_5,4H_2O$; $2Al_2O_3,3P_2O_5,10H_2O$; $Al_2O_3,3P_2O_5,6H_2O$. With the possible exception of the first, all are crystalline solids. The last is probably $H_3[Al(HPO_4)_3]$, but the constitution of the others is less certain.

Anion-exchange experiments have indicated the presence in solution of the triphosphatoaluminium complex $[Al(HPO_4)_3]^{3-}$ which, together with free phosphate, is adsorbed by the exchanger. Cation-exchange studies have indicated the existence of cationic complexes, but very little phosphate was adsorbed with the aluminium by the exchanger.

GUERIN and MARTIN (*Compt. rend.*, 1952, **234**, 1777) reported some of the results of a study of the system aluminium oxide–phosphoric oxide–water at 60°, but they gave only incomplete data. Apart from this no other systematic examination appears to have been made, although several solid aluminium phosphates have been described. Thus a tertiary phosphate, Al_2O_3,P_2O_5,nH_2O (where n has been variously ascribed the values 2, 4, 6, 7, and 8) has been described by several workers, *e.g.*, Rammelsberg (*Pogg. Ann.*, 1845, **64**, 251, 405), Wittstein (*ibid.*, 1856, **97**, 158), Millot (*Compt. rend.*, 1876, **82**, 89), Erlenmeyer (*Annalen*, 1878, **194**, 176), and Guerin and Martin (*loc. cit.*).

Three hydrates $2Al_2O_3,3P_2O_5,nH_2O$ have been reported, two of them by Guerin and Martin (*loc. cit.*), who found the values of n to be 10 and 20 respectively, and the other, for which n is 16, by Millot (*loc. cit.*) and Travers and Perron (*Ann. Chim.*, 1924, **1**, 332). In addition, a compound, $Al_2O_3,2P_2O_5,4H_2O$, has been described by Guerin and Martin (*loc. cit.*) and $Al_2O_3,3P_2O_5,6H_2O$ by Erlenmeyer (*loc. cit.*), Hautefeuille and Margottet (*Compt. rend.*, 1888, **106**, 136), Travers and Perron (*loc. cit.*), and Guerin and Martin (*loc. cit.*).

From conductivity and pH measurements on solutions containing aluminium chloride and sodium dihydrogen phosphate, Bjerrum and Dahm (*Z. physikal. Chem., Bodenstein Festband*, 1931, 627) found evidence for complexes such as $[Al(H_2PO_4)]^{2+}$, $[Al(HPO_4)]^{+}$, $[Al(H_2PO_4)_2]^{+}$, $[Al(HPO_4)_2]^{-}$, $[Al(HPO_4)_3]^{3-}$, and $[Al(H_2PO_4)_3]^{0}$. Jensen (*Z. anorg. Chem.*, 1934, **221**, 1) found the solubility of aluminium tertiary phosphate in acid solutions containing phosphate and chloride to be dependent on the phosphate concentration, but independent of the chloride-ion concentration and so concluded that pure phosphato-complexes only (and not chlorophosphato-complexes) were present in solution.

The objects of the present work have been to determine the solubility isotherm of the system aluminium oxide–phosphoric oxide–water at 25°, to determine the compositions of the stable solid phases of that system, and to ascertain the nature of the ions present in the stable solutions.

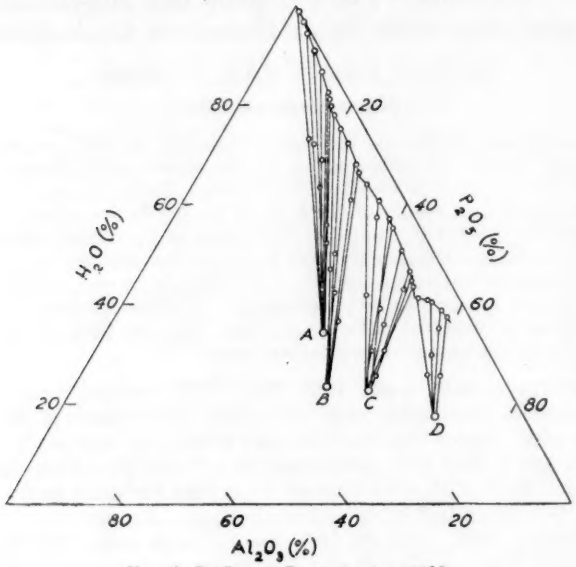
RESULTS

Phase-diagram Studies.—A study of the system at 25° for the range of solutions up to 60% of phosphoric oxide has indicated the following as the stable solid phases (Table 1 and Figure): (*A*) $Al_2O_3,P_2O_5,7H_2O$ as a microcrystalline powder, (*B*) $Al_2O_3,P_2O_5,4H_2O$ as

minute hexagonal plates, (*C*) $2Al_2O_3,3P_2O_5,10H_2O$ as small triangular plates with bevelled edges, and (*D*) $Al_2O_3,3P_2O_5,6H_2O$, as hexagonal prisms.

The degree of hydration of the two tertiary salts cannot be established accurately from the intersections of the appropriate tie-lines, but taken in conjunction with those of Guerin and Martin (*loc. cit.*) for the system at 60° our results indicate the existence of a hepta- and a tetra-hydrate. Whilst Guerin and Martin found both to occur in microcrystalline form, we have observed that the lower hydrate forms hexagonal plates.

Stable equilibria in the system, Al_2O_3–P_2O_5–H_2O *at* 25°.



For *A*, *B*, *C*, and *D*, see text p. 4013.

TABLE 1. *The system aluminium oxide–phosphoric oxide–water at* 25°.

Solutions			Moist solids			Solutions			Moist solids		
P_2O_5 (%)	Al_2O_3 (%)	$\frac{[PO_4]}{[Al]}$	P_2O_5 (%)	Al_2O_3 (%)	Type *	P_2O_5 (%)	Al_2O_3 (%)	$\frac{[PO_4]}{[Al]}$	P_2O_5 (%)	Al_2O_3 (%)	Type *
1·063	0·0791	9·64	15·89	10·68	*A*	30·96	5·08	4·38	42·31	16·03	*C*
3·016	0·2906	7·45	—	—		34·88	4·84	5·17	36·07	6·87	
4·832	0·558	6·22	17·19	10·49		38·45	4·85	5·69	46·00	15·35	
8·111	1·124	5·18	22·76	13·77		40·03	5·06	5·68	49·13	20·76	
11·23	1·984	4·06	20·01	10·96		44·16	5·60	5·66	48·55	16·04	
14·86	2·845	3·75	29·89	18·06		47·67	6·17	5·54	48·23	9·11	
15·14	3·354	3·24	27·87	16·50		49·00	6·78	5·20	52·34	22·56	
16·42	3·803	3·10 †	33·09	22·33		49·96	6·89	5·21	51·02	17·51	
17·89	4·054	3·17	33·21	19·69	*B*	51·86	7·15	5·23	61·43	13·01	*D*
20·21	4·270	3·40	32·33	17·67		53·77	5·75	6·70	—	—	
23·18	4·516	3·69	36·29	21·70		54·34	5·57	7·00	60·07	10·55	
27·12	5·150	3·78	29·54	9·62		57·21	4·64	8·86	58·88	6·64	
28·23	5·382	3·76	39·86	24·00		59·13	4·30	9·88	63·91	10·87	

* See p. 4013. † The minimum value of the mol. ratio occurs at this transition point.

The compound $2Al_2O_3,3P_2O_5,10H_2O$ was found, in agreement with Guerin and Martin (*loc. cit.*), to crystallise as small triangular plates with bevelled edges and $Al_2O_3,3P_2O_5,6H_2O$ as hexagonal prisms of varying length; Guerin and Martin describe it as crystallising as large rods.

The compound $Al_2O_3,2P_2O_5,4H_2O$ reported for the system at 60° by Guerin and Martin (*loc. cit.*) does not appear at 25°.

Anion-exchange Experiments.—The adsorption of aluminium and phosphate by Amberlite IRA-400 in the phosphate form from stable solutions (*i.e.*, of compositions decided on the basis of the solubility isotherm for 25°) has been determined under equilibrium conditions. The results are given in Table 2 *a*, and those for a corresponding series of experiments with pure phosphoric acid solutions in Table 2 *b*. A significant adsorption of aluminium by the exchanger (Table 2 *a*) indicates the presence in the aluminium phosphate solutions of anionic complexes.

TABLE 2. *Adsorption of aluminium and phosphate by* IRA-400-*phosphate* (1·000 *g.*).

(*a*) *From aluminium phosphate solutions* (100 *ml.*)

Solutions		Resin							
		Moles adsorbed/ equiv. resin :		Capacity accounted for (%) *					
P_2O_5 (%)	$\frac{[PO_4]}{[Al]}$	Al	PO_4	E	F	G	H	J	L
2	8·58	0·005	0·660	101	100	101	99	97	98
5	6·30	0·016	0·672	106	101	103	99	95	97
10	4·51	0·028	0·679	108	100	105	99	92	95
20	3·42	0·050	0·697	115	100	108	98	90	95

* Assuming the following to be adsorbed : $E = [Al(PO_4)_2]^{6-}$; $F = [Al(HPO_4)_3]^{3-}$; $G = [Al(PO_4)_2]^{3-}$; $H = [Al(HPO_4)_2]^{-}$; $J = [Al(H_2PO_4)_2(HPO_4)]^{-}$; $L = [Al(H_2PO_4)(HPO_4)_2]^{2-}$.

(*b*) *From phosphoric acid solutions* (100 *ml.*)

Solutions : P_2O_5, %	Mols. adsorbed/equiv. of resin : PO_4 (= [*y*])	Solutions : P_2O_5, %	Mols. adsorbed/equiv. of resin : PO_4 (= [*y*])
5	0·654	15	0·643
10	0·660	20	0·643

Cation-exchange Experiments.—The results of similar experiments with the hydrogen form of the cation-exchange resin Zeo-Karb 225, which are given in Table 3, show that the amount of phosphate retained by the exchanger is slight, but that this increases slowly with increasing phosphate content of the solutions. It is sufficient to indicate the presence, albeit in small amounts, of cationic complexes in the solutions.

TABLE 3. *Adsorption of aluminium and phosphate by Zeo-Karb* 225-H (0·500 g.) *from aluminium phosphate solutions* (100 ml.).

Solutions			Resin	
			Moles adsorbed/equiv. of resin :	
P_2O_5 (%)	$\frac{[PO_4]}{[Al]}$	pH	Al	PO_4
2	8·58	1·49	0·319	Nil
5	6·30	1·39	0·301	Trace
10	4·51	1·12	0·276	Trace
20	3·42	1·01	0·259	0·012

DISCUSSION

Nature of the Solutions.—Although the cation-exchange studies (Table 3) show the presence in the solutions of cationic complexes, the amount held by the exchanger is too small for the composition of the complex (or complexes) adsorbed to be determined by the method used for the cationic ferric phosphate complex (Salmon, *J.*, 1953, 2644). Nevertheless, it is significant that there is a difference in behaviour between the ferric and the aluminium phosphate system in that in the former no evidence was found for the presence of cationic complexes in pure ferric phosphate solutions (Jameson and Salmon, *J.*, 1954, 28). A further difference is that in the aluminium phosphate system the amount of aluminium adsorbed by the cation-exchanger is higher than the corresponding amount of iron adsorbed in the ferric phosphate system (Jameson and Salmon, *loc. cit.*) and rises in the more dilute solutions to the value expected for the Al^{3+} ion (namely 1/3 mole per equiv. of resin). It thus appears that there must be a higher concentration of free aluminium ions in the aluminium phosphate system than of ferric ions in the ferric phosphate system.

The adsorption of aluminium by the anion-exchanger (Table 2 *a*) is low, but an attempt has been made to account for the capacity of the resin in terms of the adsorption of free

phosphate [as a mixture of H_2PO_4' (for which 1 mole takes up 1 equiv. of resin) and HPO_4'' (0·5 mole takes up 1 equiv. of resin) ions, in the proportions indicated in Table 2 *b*] together with one of several possible anionic complexes (Table 2 *a*). The calculation, in the case of the complex $[Al(PO_4)_3]^{6-}$, for example, is made as follows: the free (*i.e.*, non-complex) phosphate is given by $[PO_4] - 3[Al]$ (where $[PO_4]$ and [Al] refer to moles adsorbed per equivalent of resin—Table 2 *a*). Then if [*y*] represents the moles of phosphate adsorbed per equivalent of resin from the phosphoric acid solutions (Table 2 *b*), the number of equivalents of exchanger taken up by the free phosphate is given by $([PO_4] - 3[Al])/[y]$. But each aluminium atom which is adsorbed as the ion $[Al(PO_4)_3]^{6-}$ takes up six equivalents of resin and hence the fraction of the capacity accounted for is $6[Al] + ([PO_4] - 3[Al])/y$ It is apparent from Table 2 *a*, in which the results have been given as percentages, that it is difficult to decide which of the possible complexes is being adsorbed; $[Al(HPO_4)_3]^{3-}$ seems most likely to be predominant, but $[Al(HPO_4)_2]^-$ is also possible. The following points, however, all suggest that it is the $[Al(HPO_4)_3]^{3-}$ ion that is adsorbed in major proportion: (1) the adsorption of phosphate is consistently above that for the phosphoric acid solutions (Table 2 *a* and *b*) which is consistent with the adsorption of $[Al(HPO_4)_3]^{3-}$ ions, for which each of the three phosphate groups effectively takes up one equivalent of resin per mole only, as compared with the value of 1·5 equivalents per mole in the case of phosphate adsorbed as simple phosphate ions [*i.e.*, the reciprocal of [*y*] in Table 2 *b*]. In the case of the adsorption of $[Al(PO_4)_2]^{3-}$ ions, on the other hand, the adsorption of phosphate should be the same as for the phosphoric acid solutions, whilst for the adsorption of $[Al(PO_4)_3]^{6-}$ ions (which might be expected by analogy with the ferric phosphate system) the adsorption of phosphate would be lower; (2) the lowest value of the ratio of phosphate to metal in the saturated solutions is almost exactly 3 (Table 1), suggesting that, as in the ferric phosphate system, a triphosphato-complex predominates (Jameson and Salmon, *loc. cit.*), in contrast to the chromic phosphate system at 40° where the ratio is 2 and the diphosphato-complex predominates (Jameson and Salmon, unpublished work) (this argument assumes that the concentration of cationic complexes is not high enough to alter the phosphate : metal ratio in solution, as in fact appears to be the case from the cation-exchange experiments); (3) the general similarity of the behaviour of the aluminium phosphate system to that of the ferric phosphate system where a triphosphato-complex $[Fe(HPO_4)_3]^{3-}$ was present (Jameson and Salmon, *loc. cit.*).

The results are in accord with those of Bjerrum and Dahm (*loc. cit.*) in indicating the presence in the solutions of both cationic and anionic complexes, but since their studies were of a system containing chloride as well as phosphate attempts at a closer correlation would not be justified.

Nature of the Solid Phases.—Little concerning the nature of the solid phases can be deduced from the present work, but the compound $Al_2O_3,3P_2O_5,6H_2O$ may be $H_3[Al(HPO_4)_3]$, since the corresponding anion appears to be present in solution.

Experimental

Preparation of Aluminium Tertiary Phosphate.—Sodium hydroxide solution was added dropwise to "AnalaR" ammonium alum (50 g.) in water (500 ml.) containing "AnalaR" syrupy phosphoric acid (10 ml.) until a permanent precipitate was just visible. The solution was filtered and the filtrate heated on a steam-bath whereupon, as a result of its negative temperature coefficient of solubility, the tertiary phosphate was precipitated. After being heated for 6 hr. the precipitate became granular. The supernatant liquor was siphoned off and replaced by 5 ml. of phosphoric acid in 500 ml. of water and the suspension was again heated for several hours. Two further treatments with water, followed by washing with boiling water on a Buchner funnel, yielded a dazzling-white solid free from sodium (by flame test). Analysis of a typical batch of the air-dried material gave the results: Al_2O_3, 32·20; P_2O_5, 44·89; H_2O, 22·90% (Calc. for $Al_2O_3,P_2O_5,4H_2O$: Al_2O_3, 32·25; P_2O_5, 44·94; H_2O, 22·81%). It was thus assumed to be the compound $AlPO_4,2H_2O$.

Preparation of Solutions for Phase-diagram Studies.—The solid tertiary phosphate was added in small amounts over a period of days with continuous (mechanical) stirring to phosphoric acid solutions of varying concentrations at 25° until no more would dissolve. Solutions thus

prepared were found to be supersaturated and hence on further stirring a solid phase separated from them. When precipitation appeared to be complete the tube was closed with a glass stopper (instead of a mercury-sealed stirrer) and the suspension left to settle for 2—3 weeks. Sometimes the initial crystallisation was slow and had to be started by gentle scratching. High viscosity seemed to be the cause of the low rate of crystallisation in most cases. The time taken for equilibrium to be reached varied from 5 to 8 weeks. The method of analysing alternate tubes in any given batch of six was employed. Two weeks were allowed to elapse between the analysis of the first and the second sets of solutions (and solids) and a smooth solubility isotherm was taken as a criterion of the attainment of equilibrium.

The method often employed in phase-diagram studies of saturating solutions at a higher temperature before cooling rapidly to the equilibrium one was not adopted since no crystals separated from such solutions, even after several months. The range of solutions studied was determined by the concentration of the commercially available " AnalaR " syrupy phosphoric acid; no attempt was made to concentrate it further.

Resins.—The strongly acidic, monofunctional cation-exchanger Permutit Zeo Karb 225 and the strongly basic monofunctional anion-exchanger Amberlite IRA-400 were used for the ion-exchange experiments. The former was in the hydrogen form and the latter in the form of its phosphate to avoid the introduction of foreign ions into the solutions on exchange.

At least three weeks, with frequent shaking, were allowed for solutions and resin to come to equilibrium. The solution was then filtered through a dry column (1-cm. internal diameter, 10 cm. long, with sintered disc of grade 2 porosity) and the filtrate kept for analysis and pH measurements. The resin was then transferred to the column and washed rapidly with water (*ca.* 50 ml.) under suction—in this way any solution adhering to the resin was quickly displaced and interaction between partly diluted solution and the resin was avoided. The column was filled with water and the resin washed with water until the washings were neutral to methyl-orange, before elution with 500 ml. of 2—3N-nitric acid. Aliquot portions of the eluate were used for analysis.

Capacity of the Resins.—The capacity of the cation-exchanger was determined by passing 250 ml. of 0·5N-sodium chloride through a column containing 0·500 g. of resin in the hydrogen form and determining the acid liberated in the effluent. For the anion-exchanger 500 ml. of 2—3N-nitric acid were passed through a column containing 1·000 g. of the chloride form of the resin and the chloride content of the effluent was determined gravimetrically. The capacities of the air-dried resins, which were determined separately on every sample of resin used, were found to be in the ranges 2·45—2·48 milliequivs./g. for IRA-400 (weighed as the phosphate form) and 3·68—3·78 milliequivs./g. for Zeo Karb 225 (hydrogen form).

Analytical Methods.—Aluminium was determined gravimetrically by means of 8-hydroxyquinoline (" oxine "). The solids were first dissolved in perchloric acid and this was also added to the solutions to prevent precipitation of phosphate on dilution. Interference by phosphate in the aluminium determination was avoided as follows: the solution was made alkaline with sodium hydroxide (added until the precipitate that formed had just redissolved), 5 ml. of a 5% solution of " oxine " in acetic acid added to the hot solution, the solution brought to the boil, and ammonium acetate solution added until precipitation was complete. The precipitate, after standing for 2 hr., was filtered off, washed, and dried in the usual way. After each analysis, the precipitate was redissolved in sulphuric acid and tested for the presence of phosphate by means of ammonium molybdate reagent.

Phosphate was determined by weighing as ammonium phosphomolybdate after drying at 115°. Efforts to separate the aluminium and phosphate by means of ion-exchange resin columns failed and the method of estimating phosphate with bismuthyl perchlorate (Salmon and Terrey, *J.*, 1950, 2813) could not be employed, since the presence of aluminium interferes with the titration. The difficulty in the ion-exchange separation was the incomplete retention of the aluminium by the exchanger—possibly caused by the high acidity required to keep the aluminium phosphate in solution.

Apparatus.—The samples, contained in Pyrex boiling-tubes fitted with B24 standard sockets to fit either stoppers or mercury-sealed stirrers, were kept at 25° ± 0·1°.

Grateful acknowledgment is made to the Governing Body of Battersea Polytechnic for the award of an Edwin Tate and Holl Scholarship to one of us (R. F. J.) and to Imperial Chemical Industries Limited for a grant.

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iso*Cyanates. Part II.* The Hofmann Reaction with C-Benzoylformamide.*

By C. L. Arcus and B. S. Prydal.

[Reprint Order No. 5621.]

From a re-investigation of the Hofmann degradation of *C*-benzoylformamide to benzoic acid and cyanate ion (cf. Rinkes, *Rec. Trav. chim.*, 1929, **48**, 960) the reaction mechanism is concluded to be that represented by expression (3) (p. 4019).

The mechanism (1) has been proposed for the Weerman degradation of α-hydroxy-amides (Part I*):

$$(1)\quad R{\cdot}CH(OH){\cdot}CO{\cdot}NH_2 \xrightarrow{ClO^-} \underset{(III)}{R{\cdot}CH(OH){\cdot}NCO} \xrightarrow{HO^-} \underset{(IV)}{R{-}\overset{\overset{O^-}{|}}{CH}{-}\overset{+}{N}{:}C{\cdot}\bar{O}} \longrightarrow R{\cdot}CHO + NCO^-$$

In the hydroxy-*iso*cyanate (III) the electron-attracting *iso*cyanate group renders the hydroxyl-hydrogen atom weakly acidic, and the anion (IV) is formed; electronic movements as shown then yield the aldehyde and cyanate ion, the reaction as a whole being an elimination.

One other Hofmann reaction has been recorded in which a substantial amount of cyanate ion is formed: Rinkes (*Rec. Trav. chim.*, 1929, **48**, 960) found, qualitatively, that the reaction of benzoylformamide with alkaline hypochlorite yields sodium benzoate and sodium cyanate; he proposed course (2) for the reaction:

$$(2)\quad Ph{\cdot}CO{\cdot}CO{\cdot}NH_2 \xrightarrow{NaOH} \underset{(V)}{Ph{\cdot}C(OH)(ONa){\cdot}CO{\cdot}NH_2} \xrightarrow{NaOCl} Ph{\cdot}C(OH)(ONa){\cdot}NCO \xrightarrow{NaOH} Ph{\cdot}CO_2Na + NaCNO$$

Anhydrous benzoylformamide (m. p. 90°, Rinkes, *loc. cit.*; m. p. 90—91°, Claisen, *Ber.*, 1879, **12**, 632) is obtained only by rigorous drying of the material prepared by acidic hydrolysis of benzoyl cyanide. By the passage of carbon dioxide through a solution of the anhydrous amide in very dilute alkali, Claisen (*loc. cit.*) obtained a material which, when air-dried, had m. p. 64—65° and gave analyses in agreement with its formulation as a monohydrate. On drying over sulphuric acid it slowly lost water. In accordance with these observations, Rinkes postulated the formation of the sodium salt of the monohydrate (V), prior to the reaction with hypochlorite. This author's course (2) for the reaction is now substantiated.

The reaction of rigorously dried *C*-benzoylformamide with aqueous alkaline hypochlorite yielded 76—81% of benzoic acid and 73—83% of cyanate (isolated as hydrazinedicarbonamide); the amide, m. p. 83—85°, which had been recrystallised but not subjected to rigorous drying, gave similar results, 78% of benzoic acid and 80—83% of hydrazine dicarbonamide.

Billeter (*Ber.*, 1903, **36**, 3218) found that benzoyl *iso*cyanate and water rapidly yield benzamide, carbon dioxide, and dibenzoylurea:

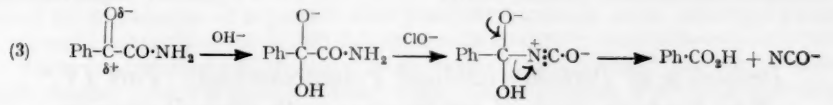
$$Ph{\cdot}CO{\cdot}NCO + H_2O \longrightarrow Ph{\cdot}CO{\cdot}NH_2 + CO_2 \ (70—75\%)$$

$$Ph{\cdot}CO{\cdot}NCO + Ph{\cdot}CO{\cdot}NH_2 \longrightarrow CO(NH{\cdot}CO{\cdot}Ph)_2 \ (25—30\%)$$

It has now been found that benzoyl *iso*cyanate reacts vigorously with aqueous alkali, to yield nearly pure benzamide (73% isolated) and only a trace of cyanate ion. The reaction resembles the alkaline hydrolysis of an alkyl *iso*cyanate to an amine: $Ph{\cdot}CO{\cdot}NCO + 2HO^- \longrightarrow Ph{\cdot}CO{\cdot}NH_2 + CO_3^{2-}$. It is apparent that benzoyl *iso*cyanate, the "normal" product of the Hofmann reaction with benzoylformamide, cannot be

* A paper entitled "The Hofmann Reaction with α- and β-Hydroxy-amides: Reactions of the Intermediate *iso*Cyanates" (Arcus and Greenwood, *J.*, 1953, 1937) is regarded as Part I.

formed during the reaction with aqueous alkaline hypochlorite. It is concluded, therefore, that interaction of benzoylformamide with hydroxyl ion precedes conversion of the amide group into *iso*cyanate, and the mechanism (3) is proposed for the complete reaction, the electronic movements being identical with those proposed for the Weerman reaction:



(3)

Experimental

C-Benzoylformamide was prepared by a modification of Claisen's method (*loc. cit.*). Concentrated hydrochloric acid (100 ml.) was saturated at 0° by the passage of hydrogen chloride; crushed benzoyl cyanide (50 g.; *Org. Synth.*, 1944, **24**, 14) was then added and the whole was shaken until a clear solution was obtained (2—6 hr.). The solution was cooled in ice and poured into water; after 1 hr. the solid was filtered off; a further quantity separated from the filtrate and was collected next day. The benzoylformamide so obtained (46 g.; m. p. 66—69°), recrystallised from ethanol, had m. p. 83—85° (Found: N, 8·65. Calc. for $C_8H_7O_2N,H_2O$: N, 8·4. Calc. for $C_8H_7O_2N$: N, 9·4%). After long drying *in vacuo* over sulphuric acid, and after being kept over phosphoric oxide at 45—50°/0·05 mm. for 1 hr., benzoylformamide had m. p. 90—90·5° (Found: N, 9·15%).

Hofmann Reaction.—Benzoylformamide [expts. (i), (ii) 2·48 g.; m. p. 90—90·5°] was added to ice-cooled, stirred alkaline hypochlorite solution (1·0N in NaOCl, 1·5N in NaOH; 67 ml.); the mixture was warmed to 34°, at which temperature the amide dissolved. Stirring was continued for 1 hr.; the excess of hypochlorite was removed by addition of aqueous sodium sulphite (36%). Semicarbazide hydrochloride (1·85 g.) was added; the solution was cooled in ice and brought to pH 3·8 by 2N-sulphuric acid; a solid commenced to separate. The whole was heated on a steam-bath for 20 min., cooled, and filtered. The precipitate was stirred for 1 hr. with cold N-sodium carbonate (50 ml.), then filtered off, washed with water, and dried. The hydrazinedicarbonamide so obtained [(i) 1·4 g., m. p. 246—247°; (ii) 1·6 g., m. p. 247—248°] had, after recrystallisation from hot water, m. p. and mixed m. p. 249—249·5°.

A control experiment, in which alkaline hypochlorite solution was successively treated with the reagents as above, gave no precipitate.

The sodium carbonate filtrate and washings were strongly acidified with 10N-sulphuric acid, and chilled; benzoic acid (*A*) separated. The filtrate from the preparation of hydrazinedicarbonamide similarly gave benzoic acid (*B*). Ether-extraction of the filtrates from (*A*) and (*B*) yielded a further quantity (*C*). Combination of (*A*), (*B*), and (*C*) gave benzoic acid [(i) 1·5 g., m. p. 119—121·5°; (ii) 1·6 g., m. p. 119·5—120·5°] which, after recrystallisation from hot water, had m. p. and mixed m. p. 121—122° (benzyl *iso*thiuronium salt, m. p. and mixed m. p. 166—166·5°).

Two similar experiments were carried out with benzoylformamide [(i), (ii) 2·48 g.] having m. p. 83—85°; in the second a double quantity of semicarbazide hydrochloride was added. There were obtained hydrazinedicarbonamide [(i) 1·5 g., (ii) 1·45 g.; each m. p. 245—246°] and benzoic acid [(i) 1·45 g., m. p. 120·5—122°; (ii) 1·45 g., m. p. 121—122°].

Benzoyl iso*Cyanate.*—A solution of benzoyl chloride (28·1 g.) in carbon tetrachloride (96 ml.; dried over P_2O_5) was added dropwise to a stirred suspension of silver cyanate (34·5 g., dried over P_2O_5 and powdered) in carbon tetrachloride (50 ml.). The whole was heated under reflux for 6 hr.; carbon tetrachloride was then distilled from the filtered solution. The product on distillation yielded benzoyl *iso*cyanate (13·6 g., 46%), b. p. 94—96°/21 mm.; it solidified on cooling. This preparation appears more satisfactory than those of Billeter (*loc. cit.*) and Hill and Degnan (*J. Amer. Chem. Soc.*, 1940, **62**, 1595) who record, respectively, b. p. 88°/10 mm. and 88—91°/20 mm.

Benzoyl *iso*cyanate (2·65 g.) was added to N-sodium hydroxide (60 ml.); a vigorous reaction occurred and a white solid separated which was filtered off and dried. It (1·6 g.) had m. p. 124—125·5°, and, after recrystallisation from hot water, m. p. and mixed m. p. 126—126·5°. A portion of the filtrate, above, was treated with pyridine, acetic acid (sufficient to render the solution acid), chloroform, and 1% aqueous copper sulphate; the chloroform layer acquired a slight blue colour, indicating a little cyanate to be present; however, on treatment of the

greater part of the filtrate with semicarbazide hydrochloride and acetic acid, an opalescence only was developed.

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Properties of Periodate-oxidised Polysaccharides. Part IV. The Products obtained on Reaction with Phenylhydrazine.*

By VINCENT C. BARRY and P. W. D. MITCHELL.

[Reprint Order No. 5572.]

Periodate-oxidised polysaccharides condense with phenylhydrazine to give amorphous products. When heated with phenylhydrazine in the presence of acetic acid, the oxypolysaccharides and their phenylhydrazine derivatives yield mixtures of osazones the separation of which has been achieved by chromatography on alumina. Thus potato oxystarch gave glyoxal bisphenylhydrazone and D-erythrosazone, and oxyxylan (*Rhodymenia palmata*) gave, in addition to the glyoxal derivative, glycerosazone and D-xylosazone. This confirms the existence of 1 : 3-linkages in this xylan. Oxidised Floridean starch gave, on the other hand, only the osazones of glyoxal and D-erythrose, and no glucosazone was detected.

DEGRADATION of oxystarch with dilute mineral acid leads to extensive changes in the molecule and has not proved of value as a method of preparation of erythrose. When the degradation is carried out with phenylhydrazine in acetic acid, much information regarding the fine structure of polysaccharides has been obtained (Barry, *Nature*, 1943, **152**, 537). The method has been applied with success to snail galactogen (O'Colla, *Proc. Roy. Irish Acad.*, 1953, **55**, *B*, 165), gum arabic (Dillon, O'Ceallacháin, and O'Colla, *ibid.*, p. 331), and nigeran (Barker, Bourne, and Stacey, *J.*, 1953, 3084). At room temperatures, phenylhydrazine forms amorphous condensation products with oxypolysaccharides (Jackson and Hudson, *J. Amer. Chem. Soc.*, 1937, **59**, 2049) and Jayme and Sätre (*Ber.*, 1944, **77**, 242, 248) used the nitrogen content of the phenylhydrazine polymer obtained from periodate-oxidised wheat straw xylan to calculate the degree of oxidation of the xylan. They formulated the oxyxylan–phenylhydrazine derivative as containing two phenylhydrazine molecules condensed on each dialdehyde group. With periodate-oxidised trehalose and raffinose, condensation is complete when one phenylhydrazine molecule has condensed for each dialdehyde group (Okui and Sujuki, *J. Pharm. Soc. Japan*, 1952, **72**, 891) and this agrees with the results obtained when isoniazid or thiosemicarbazide condenses with various oxypolysaccharides (Barry, McCormick, and Mitchell, *J.*, 1954, 3692). The phenylhydrazine–oxypolysaccharide products described in this paper appear to have a somewhat less precise composition.

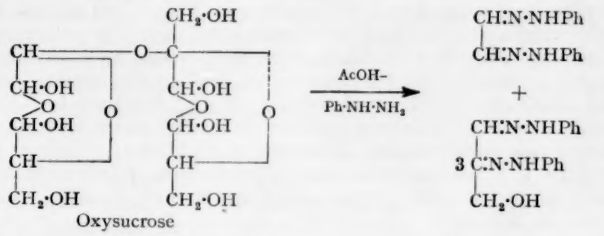
In the phenylhydrazine–acetic acid degradation experiments of oxypolysaccharides hitherto carried out, the only fragment of the molecule isolated as a crystalline derivative has been glyoxal as the bisphenylhydrazone. In general the triose and tetrose fragments seem to have been very elusive. For example, Overend, Stacey, and Wiggins (*J.*, 1949, 1358), following Jackson and Hudson (*loc. cit.*), obtained D-erythronolactone in a yield of only 7%, by hydrolysis of oxystarch with mineral acid followed by oxidation with bromine water. On the other hand, Smith and his co-workers (*J. Amer. Chem. Soc.*, 1952, **74**, 4970) have shown that reduction of oxystarch with Raney nickel or sodium borohydride followed by acid hydrolysis leads to a quantitative yield of glycollaldehyde and erythritol and suggested this proceedure as another means of investigating polysaccharide structures.

It appeared, therefore, that a successful degradation of the oxypolysaccharides would only be achieved when the aldehyde groups were protected or modified. It was of interest

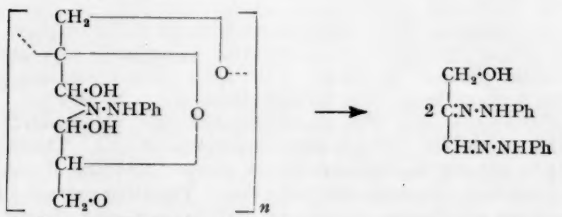
* Part III, *J.*, 1954, 3692.

for this reason to examine the Barry degradation in more detail and to determine whether the triose and the tetrose osazones could be isolated. For this purpose it was necessary to devise a method of separating osazones of low molecular weight. This was readily achieved by chromatography on alumina using benzene and benzene–ether or ether–alcohol mixtures [chromatographic separation of osazones has also been achieved by Jorgensen (*Dansk Tidsskr. Farm.*, 1950, **24**, 1), using calcium carbonate]. The products obtained by degradation of oxystarch with phenylhydrazine in acetic acid thus yielded, first, glyoxal bisphenylhydrazone and in considerable quantity; then followed D-erythrosazone which was obtained analytically pure after one recrystallisation; and then *N*-acetylphenylhydrazine, which is readily formed when phenylhydrazine is warmed with dilute acetic acid (see, *e.g.*, Andeslini, *Ber.*, 1891, **24**, 1925).

The method was next applied to the phenylhydrazine derivatives prepared from oxysucrose, oxyinulin, and oxyxylan (for formulations see *J.*, 1953, **3631**) (the xylan being obtained from *Rhodymenia palmata*; Barry, McCormick, and Mitchell, *loc. cit.*). From oxysucrose were obtained glyoxal bisphenylhydrazone and glycerosazone, while the inulin gave mainly glycerosazone together with a very small quantity of glyoxal bisphenylhydrazone. The latter could have arisen from a glucose residue at the non-reducing end of the chain.

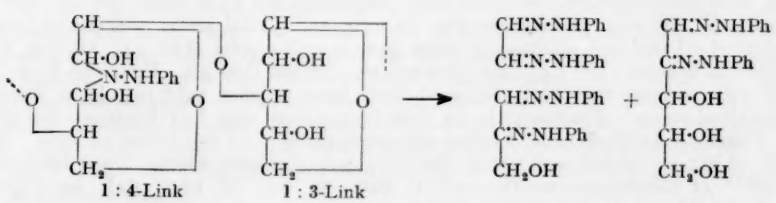


Oxysucrose



Oxyinulin phenylhydrazine polymer

The xylan, on the other hand, gave glyoxal bisphenylhydrazone, glycerosazone, and some xylosazone. The last-named osazone arises from 1 : 3-linked xylose units and suggests that some at least of the 1 : 3-linkages alternate with 1 : 4-linkages (cf. Part III, *loc. cit.*).



1 : 4-Link 1 : 3-Link

It was also found possible to separate the degradation products, rapidly and sharply, by using Rutter's circular paper chromatogram (*Nature*, 1948, **161**, 435; see also Giri, *ibid.*, 1954, **173**, 1194) and benzene(or toluene)–ethanol (9 : 1). This provides a ready method of qualitative analysis for osazone mixtures which when applied to the degradation products of the Floridean oxystarch–phenylhydrazine polymer indicated only the presence of glyoxal

bisphenylhydrazone and D-erythrosazone. No glucosazone could be detected and the conclusions reported in Part III (*loc. cit.*) regarding the structure of this starch are thus lent further support. Complete separation of the osazones could not be achieved by the usual paper chromatographic techniques, as with a variety of solvents " streaking " was always obtained.

Experimental

Rotational measurements were made in 2-dm. tubes; Brockmann standardised Merck alumina was used throughout for chromatography of the osazones.

Phenylhydrazine Derivative of Oxysucrose.—Sucrose (10·26 g.) was oxidised with sodium metaperiodate (19·5 g.) in water (300 c.c.). After being kept in the dark for 26 hr. the solution (α_D + 1·30°) was treated with lead acetate to remove iodate and periodate, and then with dilute sulphuric acid to precipitate excess of lead. The solution of oxysucrose obtained (465 c.c.) had α_D + 0·784°. 250 C.c. were treated at room temperature with phenylhydrazine (15 c.c.) in 10% acetic acid (35 c.c.). The sticky yellow solid obtained was washed well with water and dried to a yellow powder (8·52 g.), soluble in ether and alcohol, sparingly soluble in benzene, and insoluble in light petroleum. It decomposed on storage for a few days. A solution of 0·1 g. in ethanol (10 c.c.) had α_D + 0·494° ⟶ + 0·307° (5½ hr.) ⟶ + 0·29° (120 hr.).

Degradation of Oxysucrose–Phenylhydrazine Derivative.—The yellow powder (3 g.) was refluxed for 1½ hr. with phenylhydrazine (5 c.c.), 10% acetic acid (20 c.c.), and ethanol (50 c.c.). Removal of ethanol on the pump and addition of water precipitated an orange gum which was dissolved in ether and washed successively with dilute acetic acid, water, aqueous sodium hydrogen carbonate, and water. From the ether layer, a red oil (2·87 g.) was obtained which was dissolved in benzene and adsorbed on a column of alumina (50 g.). Fractions 1—3 (0·674 g.), eluted by benzene (170 c.c.), consisted of glyoxal bisphenylhydrazone which crystallised from benzene–light petroleum in pale yellow blades. Fractions 5—8 [0·223 g., eluted by benzene (310 c.c.); 0·288 g., eluted by 1 : 1 benzene–ether] were glycerosazone, which crystallised from benzene in yellow spears, m. p. 130—131° (Found: C, 67·4; H, 6·1; N, 20·7. Calc. for $C_{15}H_{14}ON_4$: C, 67·2; H, 6·0; N, 20·9%).

Phenylhydrazine Derivative of Oxystarch.—A solution (2%) of periodate-oxidised potato starch in water was treated at room temperature with an excess of phenylhydrazine in dilute acetic acid. The yellow precipitate which separated immediately was washed well with dilute acetic acid and water (Found: N, 12·55. Calc. for 1 phenylhydrazine per oxyhexose unit: N, 10·4. Calc. for 2 phenylhydrazines per oxyhexose unit: N, 16·4%).

Degradation of Oxystarch.—(a) *With phenylhydrazine only.* Oxystarch (2 g.) in water (40 c.c.) was refluxed with ethanol (130 c.c.) and phenylhydrazine (5 c.c.). The milky solution became clear and after 1½ hr. ethanol was removed at the pump. Addition of water gave a gum which together with the solution was extracted with ether. The ether extract yielded an oil (0·33 g.) which after adsorption on alumina and elution with benzene gave glyoxal bisphenylhydrazone (0·16 g.).

The solid (2·48 g.) remaining in the aqueous layer after extraction with ether was insoluble in benzene but soluble in ethanol, from which it was precipitated as an amorphous powder on addition of water. This was evidently an oxystarch–phenylhydrazine polymer as prepared above.

(b) *With phenylhydrazine and acetic acid.* Oxystarch (2·3 g.) in water (100 c.c.) was refluxed with ethanol (200 c.c.), phenylhydrazine (25 c.c.), and glacial acetic acid (30 c.c.) for 2½ hr. Removal of ethanol and addition of water gave a yellow solid (3·95 g.). Of this, 2 g. were dissolved in benzene (130 c.c.) and adsorbed on alumina (100 g.). Fractions 3—5 (1·21 g.), eluted with benzene (300 c.c.) and crystallised from benzene light petroleum, were glyoxal bisphenylhydrazone. Fractions 11—14 (0·062 g.), eluted with 1 : 1 benzene–ether (235 c.c.), were *N*-acetylphenylhydrazine, forming colourless plates from the above solvents. Fractions 18—24 (0·422 g.), eluted with ether (560 c.c.), gave feathery needles (from benzene), m. p. 175—177°, of D-erythrosazone (Found: C, 64·3; H, 6·5; N, 18·5. Calc. for $C_{16}H_{18}O_2N_4$: C, 64·7; H, 6·1; N, 18·85%).

Phenylhydrazine Derivative of Oxyinulin.—Inulin (10 g.) was oxidised for 48 hr. with sodium metaperiodate (16 g.) in water (400 c.c.). The solution which contained some undissolved material was filtered through Celite. The filtrate (420 c.c.; α_D − 3·0°) was then treated with lead acetate and dilute sulphuric acid as before and gave an iodate- and periodate-free solution (570 c.c.; α_D −1·95°) which was treated at room temperature with phenylhydrazine (15 c.c.)

in 10% acetic acid (35 c.c.). The pale yellow solid obtained weighed 10 g. (Found: N, 9·9. Calc. for oxyinulin with one phenylhydrazine molecule condensed per sugar unit: N, 10·4%). The filtrate had α_D − 0·04° and evidently the reaction was practically quantitative.

Degradation of Oxyinulin Phenylhydrazine Derivative.—The yellow powder (0·98 g.) was refluxed with ethanol (30 c.c.), phenylhydrazine (3 c.c.), glacial acetic acid (5 c.c.), and water (10 c.c.) for 4 hr. The solution, treated as previously, yielded a pale brown solid (1·91 g.) which was dissolved in benzene and adsorbed on alumina (60 g.). Fractions 1—3 (0·646 g.), eluted with benzene (240 c.c.), were a red oil, from which crystallisation from benzene–light petroleum yielded a few mg. of glyoxal osazone. Fractions 6—8 (0·339 g.), eluted by 1 : 1 benzene–ether, were glycerosazone, forming deep yellow spears, m. p. 130°, from benzene. Fractions 9—11 (0·339 g.), isolated by ether (320 c.c.), were *N*-acetylphenylhydrazine, colourless plates (from benzene–light petroleum), m. p. 127—129°.

Oxyxylan–Phenylhydrazine Derivative.—Xylan (3 g.), isolated from *Rhodymenia palmata* (Barry, McCormick, and Mitchell, *loc. cit.*), was oxidised with sodium metaperiodate (5·85 g.) in water (200 c.c.). The reaction (followed polarimetrically) was complete after 120 hr. when the solution had α_D + 2·12°. Periodate and iodate were removed as before and the oxyxylan solution obtained (360 c.c.; α_D + 1·25°) treated at room temperature with phenylhydrazine (7·5 c.c.) in 10% acetic acid (18 c.c.). The orange precipitate obtained weighed 2·53 g. (Found: N, 11·1. Calc. for each periodate-vulnerable xylose condensed with 1 phenylhydrazine molecule: N, 15·7%). The solution remaining was optically inactive.

Degradation of the Oxyxylan Derivative.—The orange powder (2·36 g.) was refluxed for 4 hr. with ethanol (60 c.c.), phenylhydrazine (7 c.c.), glacial acetic acid (9 c.c.), and water (30 c.c.). Concentration of the solution yielded crystalline glyoxal bisphenylhydrazone (1·46 g.). The filtrate on dilution with water gave a gum (2·60 g.) which was dissolved in benzene and chromatographed on alumina (80 g.), giving fractions: 1—3 (0·571 g.), eluted with benzene (130 c.c.), glyoxal bisphenylhydrazone (crystallised from benzene); 10—11, eluted with 1 : 1 benzene–ether (80 c.c.), glycerosazone (0·283 g.), forming deep yellow crystals, m. p. 130°, from benzene; 13—15 (0·462 g.), eluted by 1 : 1 benzene–ether (200 c.c.), *N*-acetylphenylhydrazine, m. p. 128° (from benzene–light petroleum); 16 (0·242 g; not crystalline), eluted by ether (150 c.c.); and 22—26 (0·346 g.), eluted by 9 : 1 ethanol–water, forming yellow needles (from methanol–water), identified as xylosazone on a circular paper chromatogram.

The solution (100 c.c.) from which the degradation products were separated had α_D − 0·416°, but no further products were isolated from it. The presence of a 1 : 3-linked oligosaccharide is therefore not ruled out.

Separation of Osazones by Circular Paper Chromatograms.—Spots of a mixture of the osazones of maltose, galactose, xylose, erythrose, glycerose, and glyoxal were made on a circle, 4 cm. in diameter, in the centre of a piece of Whatman No. 1 filter paper (30 cm. in diameter). This was clamped between two glass plates and eluted with a mixture of toluene, ethanol, and water (270 : 30 : 1) by means of a wick inserted into the centre of the paper. Separate spots of the osazones of arabinose, glucose, and rhamnose were run concurrently. After 2 hr. the osazones had separated into well-defined arcs which were easily visible. They may be darkened by spraying with ammoniacal silver nitrate. The R_F values were found to vary somewhat along different axes. The average values of a number of runs in different directions were as follows: glyoxal 0·96, glycerose 0·75, erythrose 0·55, rhamnose 0·54, arabinose 0·48, xylose 0·47, galactose 0·42, glucose 0·41, and maltose 0·046.

This method of identification was very useful as a rapid analysis of the products of the degradation of the oxypolysaccharides. It was necessary to keep the time of heating with phenylhydrazine to a minimum (15—30 min.) to avoid the formation of much *N*-acetylphenylhydrazine since this appeared as a spot at about the same point as erythrosazone and obscured this osazone especially when the paper was developed with ammoniacal silver nitrate. When this method was applied to the Floridean oxystarch–phenylhydrazine derivative prepared in the usual way, no evidence of glucosazone was obtained, whilst spots due to the osazones of D-erythrose and glyoxal were visible. Similarly the xylan derivative gave clear evidence of xylosazone, glycerosazone, and glyoxalosazone.

One of us (P. W. D. M.) is indebted to University College, Dublin, for a Lasdon Foundation Research Fellowship.

LABORATORIES OF THE MEDICAL RESEARCH COUNCIL OF IRELAND,
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Oxidation of Glycerol by Periodate in Alkaline Solution.

By L. HARTMAN.

[Reprint Order No. 5379.]

WHEN oxidizing glycerol with periodate in N-sodium hydroxide at 30° Fleury and Fatome (*J. Pharm. Chim.*, 1935, **21**, 247) observed an apparent regeneration of periodate, its consumption amounting to 32% of the theoretical value after ½ hr., 16% after 4 hr., and 90% after 48 hr. Lundblad (*Arkiv Kemi, Min. Geol.*, 1947, **24**, *A*, No. 25) attributed this regeneration to the method used by Fleury and Fatome for estimating the excess of the oxidizing reagent, *viz.*, reduction of periodate to iodate with standard arsenite solution and potassium iodide in a sodium hydrogen carbonate buffer, and titration of the excess of arsenite with iodine solution (Fleury and Lange, *J. Pharm. Chim.*, 1933, **17**, 107). According to Lundblad, di- and tri-sodium paraperiodates which were formed and partly settled out under the condition of the experiment did not react with arsenite, and thus escaped determination. Furthermore, " blanks " varied with time, and over-oxidation was observed after 15 hr. However, if the excess of periodate was determined by the addition of potassium iodide and sulphuric acid the oxidation proceeded normally and was complete in 48 hr.

Lundblad's results, amongst others, imply that the reaction between arsenite and periodate is not quantitative. This could not be confirmed in the present work, and no definite " regeneration " of periodate was observed whether the excess of reagent was estimated by the arsenite or by the potassium iodide–sulphuric acid method. The reproducibility of periodate estimation in " samples " was admittedly poor, but " blanks " were constant.

It is suggested that the conflicting results, summarized in Table 1, are due, at least in part, to the complex mechanism of oxidation by periodates in alkaline solution. This

TABLE 1. *Oxidation of glycerol with sodium periodate at* pH 13, *at* 30°.

	Consumption of $NaIO_4$ (mol./mol. of glycerol) (Theor. 2 mols./mol.)				
				Present work	
	Fleury & Fatome	Lundblad		Results from various batches of periodates	
Time (hr.)	Arsenite	Arsenite	KI–H_2SO_4	Arsenite	KI–H_2SO_4
(5 min.)	—	0·34	—	0—0·21	0
(8 min.)	0·39	—	0·17	0—0·15	0
0·25	1·26	0·30	0·21	0·08—0·15	0·15—0·24
0·5	1·29	0·45	0·24	0·14—0·32	0·22—0·35
1	1·07	0·51	0·29	0·18—0·33	0·30—0·35
2	—	0·27	0·40	0·21—0·49	0·37—0·67
4	0·65	0·61	0·53	0·35—0·41	0·45—0·71
8	—	0·83	—	0·40—0·56	0·49—0·88
15	1·41	2·20	0·88	0·53—1·06	0·92—1·39
22	—	2·04	—	0·57—1·03	0·99—1·40
36	—	—	1·66	1·31—1·58	1·65—1·91
48	1·78	2·79	2·03	1·50—2·02	1·82—2·34

complexity, established, for instance, for cellulose (Davidson, *J. Text. Inst.*, 1941, **32**, T 109; Head, *ibid.*, 1947, **38**, T 389), seems to apply also to the oxidation of glycerol. Already at a comparatively early stage of the reaction the occurrence of secondary reactions was observed. These consist, amongst others, in the oxidation of one of the primary reaction products, formaldehyde, to formic acid. On the basis of the overall consumption of periodate the oxidation of glycerol is apparently complete in about 48 hr. (cf. Table 1) but, if secondary reactions are considered, seems to extend over a period of about 7 days (cf. Table 2). Photosensitivity (Head and Hughes, *J.*, 1952, 2046) might be also responsible for the differing results shown in Table 1. Photochemical interference was avoided in the present work by the use of amber-glass reaction bottles, but possibly previous investigators did not take this precaution.

In view of the difficulty of studying the kinetics of glycerol oxidation in strongly alkaline solutions, the study of this reaction in a sodium hydrogen carbonate buffer appears more convenient. No over-oxidation was noted under these conditions and the agreement between the results obtained by Fleury and Fatome (*loc. cit.*) and in the present work was quite satisfactory (cf. Table 3).

TABLE 2. *Consumption of periodate by glycerol and by secondary reactions.*

	Consumption of $NaIO_4$ (mol./mol. of glycerol)			
	Observed		Calculated	
Time (hr.)	After stopping reaction with $KI–H_2SO_4$	After oxidizing residual glycerol	For glycerol	For secondary reactions
1	0·30	2·03	0·27	0·03
2	0·37	2·12	0·25	0·12
4	0·71	2·17	0·54	0·17
6	0·78	2·17	0·61	0·17
12	1·02	2·18	0·84	0·18
(days)				
1	1·51	2·44	1·07	0·44
2	2·34	2·69	1·65	0·69
3	2·54	2·94	1·60	0·94
4	2·90	3·09	1·81	1·09
5	3·14	3·27	1·87	1·27
6	3·31	3·45	1·86	1·45
7	3·55	3·59	1·96	1·59

TABLE 3. *Consumption of* $NaIO_4$ *(mol./mol.) on oxidation of glycerol at* pH 8·5 *and* 30°.

Time (min.)	5	10	15	30	45	60	90	150	180
Fleury & Fatome [a]	1·04	1·36	1·62	1·84	1·88	1·92	1·95	1·98	2·0
Present work [b] ...	0·83	1·27	1·68	1·86 *	1·91	1·94 *	1·98	1·99	1·99 *†

[a] Arsenite. [b] $KI–H_2SO_4$.
* No consumption in secondary reactions. † After 24 hr., 1·99.

Experimental.—The experiments were carried out at 30°, the quantity of reactants being as specified by Fleury and Fatome, *i.e.*, 0·01M-glycerol 10 ml., 2N-sodium hydroxide 15 ml., and 0·1M-periodic acid 5 ml. The reaction was stopped with sodium arsenite and potassium iodide or with potassium iodide and sulphuric acid severally.

The consumption of periodate by glycerol and by secondary reactions was assessed as follows: Sets of 2 "samples" and 1 "blank" were held at 30° for various periods. At appropriate intervals one sample of each set was acidified with N-sulphuric acid and left for 15 min. in order to oxidize the residual glycerol. Potassium iodide solution (2 ml. of 30%) and an excess of sulphuric acid were then added and the mixture was titrated with sodium thiosulphate. In the second sample the reaction was stopped with potassium iodide and sulphuric acid, titration being with sodium thiosulphate. The amount of periodate consumed by glycerol and by secondary reactions was then calculated (cf. Table 2) by assuming that the reduction of periodate which took place after the acidification of the first sample was caused solely by the residual glycerol. Some indication of the nature of the secondary reactions was obtained by determining the concentration of formaldehyde by dimedone (Reeves, *J. Amer. Chem. Soc.*, 1941, **63**, 1476) in samples kept at 30° for 24 hr. or more. This concentration was always lower than expected from the amount of glycerol consumed, but was not reproducible. Other changes such as oxidation of formic acid to carbon dioxide and water probably occurred simultaneously.

Results shown in Table 3 were obtained by proceeding as in the main set of experiments except that 15 ml. of M-sodium hydrogen carbonate solution were used instead of sodium hydroxide.

The quantitative character of the reaction between periodate and arsenate was confirmed by testing a number of commercial samples of periodic acid and its sodium salts under various conditions (with and without previous addition of sodium hydroxide, without delay and after several days' storage at 30°). Most samples contained appreciable amounts of iodate, but in each case there was close agreement between the estimation of the actual periodate content by the arsenite and by the potassium iodide and sulphuric acid methods.

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Reactions of Metallic Salts of Acids. Part V. Synthesis of Fluoro-dienes from Fluoro-dicarboxylic Acids.*

By R. N. HASZELDINE.

[Reprint Order No. 5382.]

MANY fluoro-dicarboxylic acids of general formula $[CF_2]_n(CO_2H)_2$ (see Haszeldine and Sharpe, " Fluorine and its Compounds," Methuen, 1951) are available for use in synthetic fluorine chemistry. The present communication describes methods for the conversion of these into fluoroalkadienes, and in particular describes the conversion of the compound where $n = 4$ into hexafluorobutadiene.

Pyrolysis of anhydrous disodium octafluoroadipate at 100—350° yields two major volatile fractions and a residue of sodium fluoride and carbon. The more volatile fraction contains carbon dioxide, carbonyl fluoride, hexafluorobutadiene, and, probably, acyl fluorides formed by breakdown of the carbon chain. The formation of hexafluorobutadiene can be visualised as follows :

$$NaO_2C{\cdot}[CF_2]_4{\cdot}CO_2Na \longrightarrow {}^-O_2C{\cdot}CF_2{\cdot}CF_2{\cdot}CF_2{\cdot}CF_2{\cdot}CO_2^- \xrightarrow{-CO_2} {}^-CF_2{\cdot}CF_2{\cdot}CF_2{\cdot}CF_2^-$$

$$^-CF_2{-}CF{-}CF{-}CF_2^- \longrightarrow CF_2{:}CF{\cdot}CF{:}CF_2 + 2F^-$$

i.e., formation of a fluorocarbanion followed by elimination of fluoride. A similar mechanism has been proposed for the formation of perfluoroalk-1-enes by the pyrolysis of sodium salts of perfluoro-monocarboxylic acids (Haszeldine, *J.*, 1952, **4259**, **3423**; *Nature*, 1951, **168**, 1028, where other evidence for fluorocarbanion instability is summarised; see also Hals, Reid, and Smith, *J. Amer. Chem. Soc.*, 1951, **73**, 4054). The yields of conjugated fluoroalkadienes prepared in this way (*ca.* 30%) are less than those of the perfluoroalk-1-enes (*ca.* 80%). Alternative routes to hexafluorobutadiene have been described in another series (*J.*, 1952, 4423).

The production of hexafluorobutadiene does not necessarily involve the simultaneous formation of both double bonds in the molecule, since fluoride elimination could occur first from a carbanion at one end of the chain and then from a carbanion at the other end of the chain :

$$^-O_2C{\cdot}[CF_2]_4{\cdot}CO_2^- \xrightarrow{-CO_2} {}^-O_2C{\cdot}[CF_2]_3{\cdot}CF_2^- \longrightarrow {}^-O_2C{\cdot}[CF_2]_2{\cdot}CF{:}CF_2 \xrightarrow{-CO_2}$$

$$^-CF_2{\cdot}CF_2{\cdot}CF{:}CF_2 \longrightarrow C_4F_6$$

Some support for this is given by the isolation of 2 : 2 : 3 : 3 : 4 : 5 : 5-heptafluoropent-4-en-1-oic acid (I) by hydrolysis of the less-volatile products from the pyrolysis of sodium octafluoroadipate; that these products contain an acyl fluoride with a $\cdot CF{:}CF_2$ group

$$[CF_2]_4(CO_2Na)_2 \longrightarrow CF_2{:}CF{\cdot}CF_2{\cdot}CF_2{\cdot}COF \longrightarrow \underset{\text{(I)}}{CF_2{:}CF{\cdot}CF_2{\cdot}CF_2{\cdot}CO_2H}$$

is shown by spectroscopic detection of the C:O and C:C vibrations. The formation of acyl fluorides is not unexpected, since Swarts (*Bull. Acad. roy. Belg.*, 1922, **8**, 343) showed that trifluoroacetyl fluoride is a product of the pyrolysis of sodium trifluoroacetate.

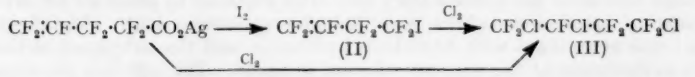
Unsaturated fluoro-carboxylic acids can also by converted into fluoro-dienes in good yield by the sodium-salt reaction, *e.g.*;

$$CF_2{:}CF{\cdot}CF_2{\cdot}CF_2{\cdot}CO_2Na \longrightarrow CF_2{:}CF{\cdot}CF{:}CF_2$$

This reaction, and the fact that the acid (I) or the crude acyl fluoride yields perfluorosuccinic acid when oxidised, establish the constitution of the heptafluoropentenoic acid. Comments on the m. p. of perfluorosuccinic acid are made on p. 4027.

* Parts I, III, and IV, *J.*, 1951, 584; 1952, 4259; 1953, 4172.

The unsaturated acid (I) readily yields a silver salt which, on reaction with iodine (cf. Parts I and III *) gives heptafluoro-4-iodobut-1-ene (II), and on reaction with an excess of chlorine yields 1 : 2 : 4-trichloroheptafluorobutane (III); chlorination of the iodo-compound also yields (III).



Perfluoroadipic acid can thus be used as a convenient source of substituted butanes, butenes, and butadienes, and the extension of the above reactions to other polycarboxylic fluoro-acids will be described later.

Experimental

Pyrolysis of sodium octafluoroadipate. Octafluoroadipic acid, prepared by oxidation of perfluoro*cyclo*hexene with permanganate (Tatlow and Worthington, *J.*, 1952, 1251; Haszeldine, *Nature*, 1951, **168**, 1028), was converted into the disodium salt by neutralisation with aqueous sodium hydroxide. The salt, isolated by evaporation of the aqueous solution to dryness *in vacuo*, was ground in a mortar and thoroughly dried at 120° *in vacuo*. Sodium octafluoroadipate (5·0 g., 0·015 mole) was spread in a thin layer in a horizontal open cylinder of platinum foil which was then inserted into a horizontal nickel furnace tube 1" in diameter and sealed at one end. The tube was evacuated to 10^{-2} mm. and then heated stepwise (2·5 hr.) to 450°. Two glass traps connected in series between the furnace tube and the pump were examined periodically; appreciable reaction occurred below 300°; there was little sign of further reaction at temperatures above 370°. The solid residue from the pyrolysis contained sodium fluoride, carbon, and carbonaceous material.

The combined volatile products were transferred to a vacuum system where they were arbitrarily separated into fractions boiling above or below 10°. Infra-red spectroscopic examination of the more volatile fraction showed it to contain hexafluorobuta-1 : 3-diene, contaminated by carbon dioxide, carbonyl fluoride, and by material (probably acyl fluorides) which showed carbonyl absorption at 5·3 μ. The fraction was washed with 2N-sodium hydroxide and refractionated *in vacuo* to give hexafluorobutadiene (0·73 g., 30%), b. p. 5·7° (Found: C, 29·7%; *M*, 162. Calc. for C_4F_6: C, 29·6%; *M*, 162). The b. p. and infra-red spectrum of the purified material were identical with those reported by the author (*J.*, 1952, 4423). In other experiments the yields of hexafluorobutadiene were 32, 37, and 25%. The diene did not contain perfluoro*cyclo*butene.

Infra-red spectroscopic examination of the less volatile fraction (*M*, 240; cf. CF_2:$CF{\cdot}CF_2{\cdot}CF_2{\cdot}COF$, *M*, 228) showed it to contain the $-CF_2{\cdot}COF$ group (C:O absorption at 5·31 μ; cf. $CF_3{\cdot}COF$ 5·25 μ; $C_2F_5{\cdot}COF$ 5·29 μ, $C_3F_7{\cdot}COF$ 5·3 μ) and the $-CF$:CF_2 group (C:C absorption at 5·6 μ; cf. $CF_3{\cdot}CF$:CF_2 5·56 μ, $C_2F_5{\cdot}CF$:CF_2 5·56 μ; *J.*, 1952, 4423, 4259). The fraction was shaken with water (5 ml.) in a sealed tube (20 min.), to leave only a small unidentified fraction (0·05 g.), b. p. 60° (isoteniscope) (Found: *M*, 275). The main bulk of the fraction had dissolved, with liberation of fluoride ion; the aqueous solution was extracted with ether (10 × 3 ml.). The ethereal solution was dried (Na_2SO_4), and after removal of the ether the residual liquid was distilled from a small amount of phosphoric anhydride through a short column to give 2 : 2 : 3 : 3 : 4 : 5 : 5-*heptafluoropent-4-en-1-oic acid* (0·69 g., 21% based on sodium octafluoroadipate), b. p. 75—76°/59 mm. (Found: C, 26·4; H, 0·5%; equiv., 226. $C_5HO_2F_7$ requires C, 26·6; H, 0·4%; equiv., 226), and unidentified material of higher b. p. The infra-red spectrum of the acid showed a band at 5·62 μ revealing the presence of the carboxyl group; the C:C stretching absorption is combined with this band.

Oxidation of the pentenoic acid (0·2 g.) by potassium permanganate, as for the oxidation of compounds which contain the $\cdot CF$:CF_2 group (*J.*, 1952, 4259), gave perfluorosuccinic acid (53%), m. p. 116°, identified by comparison of its infra-red spectrum with that of an authentic specimen. The same acid was obtained (58%) (Found: C, 25·0; H, 1·0%; equiv., 95. Calc. for $C_4H_2O_4F_4$: C, 25·3; H, 1·1%; equiv., 95) by oxidation of a specimen (0·4 g.) of the original crude acyl fluoride of the heptafluoropentenoic acid. Perfluorosuccinic acid shows carbonyl absorption in the infra-red at 5·65 μ (cf. $CF_3{\cdot}CO_2H$ 5·60, $C_2F_5{\cdot}CO_2H$ 5·64, $C_3F_7{\cdot}CO_2H$ 5·61, $C_9F_{19}{\cdot}CO_2H$ 5·68 μ). Henne and Zemmerschied (*J. Amer. Chem. Soc.*, 1947, **69**, 281) reported m. p. 86·4—87·4° for an acid which had apparently the correct equivalent for perfluorosuccinic acid, but Padbury and Kropa (U.S.P. 2,502,478) reported m. p. 116—119°.

Buxton, Ingram, Smith, Stacey, and Tatlow (*J.*, 1952, 3830) confirmed Padbury and Kropa's results, but stated that intensive drying was essential to obtain a m. p. of 116°. In our experience intensive drying is not essential if the acid is distilled *in vacuo* from a small amount of phosphoric anhydride (*ca.* 5% of that theoretically required to form the cyclic anhydride); the m. p. drops to that of the hydrate (86°) only after exposure to moist air for several hours.

Preparation of hexafluorobutadiene from heptafluoropentenoic acid. Heptafluoropentenoic acid (1·02 g.) was neutralised with 5N-sodium hydroxide, and the anhydrous sodium salt was obtained by evaporation of the aqueous solution *in vacuo*. The salt was powdered, re-dried at 120°/10^{-2} mm., placed in the platinum cylinder as described above, and pyrolysed by raising the temperature from 160° to 450° (4·5 hr.) at 10^{-2} mm. The residual sodium fluoride contained only a small amount of carbon. The volatile products were shaken in a sealed tube with 2N-sodium hydroxide, then fractionated *in vacuo* to give hexafluorobuta-1 : 3-diene (61%), identified by means of its infra-red spectrum.

The hexafluorobutadiene prepared by the methods described above was mixed with a slight excess of chlorine and exposed to ultra-violet light (1 hr.) to give, by absorption of two molecular equivalents of chlorine, 1 : 2 : 3 : 4-tetrachlorohexafluorobutane (91%), b. p. 131—133°, spectroscopically identical with the compound previously described (*J.*, 1952, 4423).

Heptafluoro-4-iodobut-1-ene. Heptafluoropentenoic acid (1·2 g.), prepared as described above, was treated with a slight excess of freshly prepared silver carbonate. Evaporation of the aqueous solution to dryness *in vacuo* yielded *silver* 2 : 2 : 3 : 3 : 4 : 5 : 5-*heptafluoropent-4-en-1-oate* (97%) (Found: Ag, 32·2. $C_5O_2F_7Ag$ requires Ag, 32·4%) as a white crystalline solid. The silver salt (1·5 g.) was mixed with a 300% excess of powdered dry iodine in a silica flask connected *via* pressure tubing to two traps cooled by liquid oxygen. The pressure was maintained at 300 mm., and the solid was heated by a small flame. The gases evolved by the smooth reaction were pumped into the traps, and the combined volatile material was washed with 2N-sodium hydroxide in a sealed tube. The residual organic material was distilled *in vacuo* to give *heptafluoro-4-iodobut-1-ene* (72%), b. p. (isoteniscope) 20°/65 mm., *ca.* 70°/760 mm. (Found: C, 15·4%; *M*, 309. C_4IF_7 requires C, 15·6%; *M*, 308). At higher temperatures there was some reaction with the mercury of the isoteniscope, and the b. p. at 760 mm. is subject to error. The compound shows a band at 5·6 μ in the infra-red.

Heptafluoro-4-iodobut-1-ene (0·7 g.) and a 10% excess of chlorine in a sealed silica tube exposed to ultra-violet light (2 days) gave iodine trichloride and 1 : 2 : 4-*trichloroheptafluorobutane* (83%), b. p. 96—97° (micro) (Found: C, 16·8%; *M*, 285. $C_4Cl_3F_7$ requires C, 16·7%; *M*, 287·5). The same compound was obtained (66%) by reaction of an excess of dry chlorine with silver heptafluoropentenoate (1·1 g.) in a sealed tube at 100° for 4 hr.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, May 13th*, 1954.]

The Esterifying Acids of Lycoctonine Alkaloids.

By R. C. COOKSON, J. E. PAGE, and M. E. TREVETT.

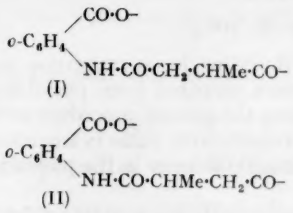
[Reprint Order No. 5419.]

BY hydrolysis with acid to lycoctonine and acetic and anthranilic acid, and with alkali to lycoctonine and *N*-acetylanthranilic acid (Goodson, *J.*, 1944, 108) ajacine was shown to be a *N*-acetylanthranilic ester of the trihydroxy-alkamine, lycoctonine. Methyl-lycaconitine, similarly, yields lycoctonine and (−)-methylsuccinic and anthranilic acid on acid hydrolysis, and lycoctonine and (−)-methylsuccinylanthranilic acid on alkaline hydrolysis (Goodson, *J.*, 1943, 139).

Methyl-lycaconitine seems to have been tacitly assumed to be a diester-amide (I or II), but we have now obtained decisive evidence in favour of the alternative monoester-imide structure (III).

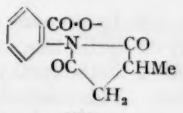
Ajacine and methyl-lycaconitine both react with periodic acid at about the same rate as lycoctonine (although reaction does not cease after consumption of 1 mol.), so that the α-glycol group of the alkamine (Edwards and Marion, *Canad. J. Chem.*, 1954, **32**, 195) must be free in both ester alkaloids, in which therefore only the primary alcohol group (*idem, ibid.*, 1952, **30**, 627) can be esterified. The presence of the monoester-imide grouping (III) in methyl-lycaconitine is confirmed by spectroscopic evidence. The ultra-

violet absorption spectrum of the alkaloid (max. at 230 and 273 mμ; ε 15,300 and 3500 respectively) differs markedly from that of ajacine (max. at 223, 252, 310 mμ; ε 28,400, 16,600, and 5400 respectively), which is identical with that of methyl *N*-acetylanthranilate. The shift of absorption to shorter wave-lengths than that shown by the two known



(I)

(II)



(III)

acetylanthranilic esters is in line with structure (III). Conclusive evidence was provided by the infra-red spectra (see Table). That of methyl-lycaconitine lacks the low-frequency

Infra-red absorption frequencies (*cm.*$^{-1}$, *in* CS_2).

Compound	NH	Amide	Imide	Ester
Methyl *N*-acetylanthranilate	3310 (m)	1692 (s)	—	1712 (s), 1262 (s)
Ajacine dihydrate	3320 (m)	1690 (s)	—	1710 (s), 1256 (s)
N-Phenylsuccinimide	—	—	1725 (s), 1786 (w)	—
Methyl-lycaconitine	—	—	1722 (s), 1787 (w)	1722 (s), 1256 (s)
,, ...	—	—	1720 (s), 1785 (w) *	1720 (s), 1265 (s) *

* In Nujol. s = Strong, m = medium, w = weak; — denotes absence of an absorption peak.

amide-carbonyl stretching band (*ca.* 1690 cm.$^{-1}$) shown by *N*-acylanthranilates; instead, a very strong absorption peak, due to the superimposed C=O stretching frequencies of the amide and the ester group, appears at *ca.* 1720 cm.$^{-1}$. The characteristic, though relatively weak, high-frequency imide band (*ca.* 1785 cm.$^{-1}$) also occurs in the spectrum of methyl-lycaconitine. The absence of CO·NH in methyl-lycaconitine is revealed by the transparency of the alkaloid near 3320 cm.$^{-1}$, where the N–H stretching frequency of ajacine occurs, and (in Nujol) near 1560 cm.$^{-1}$, where the C–N stretching peak of secondary amides is found (Letaw and Gropp, *J. Chem. Phys.*, 1953, **21**, 1621, and earlier papers listed there). Lycoctonine hydrate does not, of course, absorb in the C=O stretching region.

Experimental.—Measurements of ultra-violet absorption were made in absolute ethanol with a Unicam SP 500 Spectrophotometer and of infra-red absorption with a Model 21 Perkin-Elmer double-beam spectrophotometer.

Lycoctonine hydrate and ajacine dihydrate were pure recrystallised samples. Methyl-lycaconitine was isolated from its crystalline hydriodide by treatment with sodium hydrogen carbonate solution and extraction with chloroform. Evaporation of the washed chloroform extract at reduced pressure left the free base as a colourless froth, which was dried at 50° *in vacuo*.

Periodic acid titrations. The alkaloid (*ca.* 25 mg.) was dissolved in freshly prepared periodic acid solution (5 ml.: *ca.* 0·54M), and the mixture, made up to 10 ml. with water, was stored in the dark. At daily intervals, 1-ml. portions were pipetted into water (5 ml.) and 0·10N-sodium arsenite (1 ml.) containing potassium iodide (*ca.* 50 mg.). After 15 min. the mixture was titrated with 0·020N-iodine (starch indicator). The spontaneous deterioration of a blank solution of periodic acid was followed at the same time (cf. Jackson, *Org. Reactions*, 1944, **2**, 341). Up-takes of periodic acid (mols.) at daily intervals were:

Lycoctonine	0·82	0·96	1·11	1·33	1·40	1·74
Ajacine	0·42	0·57	0·81	1·00	1·23	1·44
Methyl-lycaconitine	0·44	0·49	0·65	0·70	0·98	1·12

We are indebted to the Central Research Fund of London University for a grant for purchase of *Delphinium* seed.

Birkbeck College, London, W.C.1.
Glaxo Laboratories Ltd., Greenford, Middlesex.

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Naphthyridines. Part II. The Attempted Cyclisation of Schiff's Bases.*

By E. P. Hart.

[Reprint Order No. 5441.]

During attempts to prepare unknown naphthyridine bases, attention was directed to the possibility of cyclisation of the Schiff's bases prepared from pyridine-aldehydes and aminoacetal (2 : 2-diethoxyethylamine), following the general procedure of the Pomeranz–Fritsch reaction. This reaction has proved of considerable value in *iso*quinoline syntheses, the cyclisation being carried out with sulphuric acid, alone or in the presence of phosphoric oxide or phosphoryl chloride.

In the present work aminoacetal was heated with the pyridine-aldehydes and with quinoline-2-aldehyde, giving in high yield Schiff's bases of type (I; R = pyridyl). Attempted cyclisation of these anils in sulphuric acid, alone or in the presence of phosphoryl chloride and phosphoric oxide resulted only in the cleavage of the azomethine system. The action of boron trifluoride upon these Schiff's bases resulted in formation of dark-brown resins from which no substance was isolated. Andersag ("Medicine in its chemical aspects," I.G. Farbenind., Leverkusen, 1934, Vol. II) states that nitrobenzylideneamino-acetal (I; R = $O_2N{\cdot}C_6H_4$) does not cyclise in sulphuric acid, but gives no experimental details. We have consequently prepared the *m*- and the *p*-nitrobenzylideneamino-acetal and confirmed the statement that cyclisation does not occur. Hey and Williams (*J.*, 1951, 1528) report an abortive attempted cyclisation of the *o*-3-pyridylbenzylideneamino-acetal (I; R = *o*-3-$C_5H_4N{\cdot}C_6H_4$) by using sulphuric acid, phosphoryl chloride, or anhydrous hydrogen fluoride.

Application of the Pomeranz–Fritsch reaction to the preparation of thionaphthenopyridines was reported by Herz and Tsai (*J. Amer. Chem. Soc.*, 1953, **75**, 5122), who found that while the use of sulphuric acid was not successful, a mixture of polyphosphoric acid and phosphoryl chloride gave the required product. We have found in the present work that while benzylideneaminoacetal affords *iso*quinoline with this mixture, the Schiff's bases from pyridine-aldehydes and from quinoline-2-aldehyde did not cyclise to form naphthyridines, and the nitrobenzylideneaminoacetals did not cyclise to nitro*iso*quinolines.

$R{\cdot}CH{:}N{\cdot}CH_2{\cdot}CH(OEt)_2$
(I)

Experimental.—Schiff's bases. The aldehyde (2 g.) and aminoacetal (2 ml.) were heated (water-bath) for 2 hr., during which time water separated. The residual mixture was dissolved in ethanol, dried (Na_2SO_4), and distilled *in vacuo*. The Schiff's bases obtained by this method are given in the following Table and these, with the exception of the one prepared from *p*-nitrobenzaldehyde, were pale straw-coloured oils when freshly prepared, rapidly darkening on exposure to air.

				Found (%)			Required (%)		
R in (I)	Yield (%)	B. p./mm.	Formula	C	H	N	C	H	N
2-Pyridyl	77	160°/11	$C_{12}H_{18}O_2N_2$	64·4	8·35	12·3	64·8	8·2	12·5
3-Pyridyl	75	170°/11	,,	65·0	8·25	12·3	64·8	8·2	12·5
4-Pyridyl	75	170°/14	,,	64·3	8·25	12·3	64·8	8·2	12·5
2-Quinolyl	72	235°/13	$C_{16}H_{20}O_2N_2$	69·9	7·6	10·4	70·4	7·4	10·3
m-Nitrophenyl	77	208°/14	$C_{13}H_{18}O_4N_2$	58·5	6·9	10·2	58·6	6·8	10·5
p-Nitrophenyl	60	M. p. 51—52 [a]	,,	58·5	6·8	10·2	58·6	6·8	10·5

[a] Twice recrystallised from aqueous ethanol.

iso*Quinoline.* Phosphoric oxide (6 g.) was added slowly to syrupy phosphoric acid (6 g.) followed by phosphoryl chloride (1 ml.). Benzylideneaminoacetal (2 g.) was then added and the temperature maintained at 140° for 2 hr. The viscous residue was poured into a small volume of water, and extracted with ether. The aqueous portion of this extract was basified with potassium hydroxide, and extracted with ether. Distillation of the dried extract afforded *iso*quinoline (0·6 g.), b. p. 240—241°.

* Part I, *J.*, 1954, 1879.

Attempted cyclisations. With the mixture of polyphosphoric acid and phosphoryl chloride prepared as in the previous experiment, and at temperatures varying between 140° and 160°, the Schiff's bases prepared in this work yielded only the corresponding aldehydes.

I am indebted to Dr. E. Tittensor for his interest and advice, and to Dr. F. L. Rose, O.B.E., Imperial Chemical Industries Limited, Dyestuffs Division, for assistance with the preparation of aminoacetal. This work was in part aided by a grant from the Research Fund of the Chemical Society.

THE TECHNICAL COLLEGE, NOTTINGHAM. [*Received, June 4th,* 1954.]

The Preparation and Structure of a Synthetic Polyglucose.

By C. R. RICKETTS.

[Reprint Order No. 5478.]

IT has long been known that the acidic hydrolysis of polysaccharides to simpler sugars is to some extent a reversible reaction and there are numerous references to the structure of the saccharides thus formed (*e.g.*, Thompson, Anno, Wolfrom, and Inatome, *J. Amer. Chem. Soc.*, 1954, **76**, 1309). Pacsu and Mora (*J. Amer. Chem. Soc.*, 1950, **72**, 1045) briefly report the isolation of saccharides containing up to 42 anhydroglucose units, but give no details. The essence of their process is to evaporate a solution of glucose in hydrochloric acid; thereby the molecules of glucose may be pictured as being brought nearer together in the presence of acid and bonds are formed between them. An alternative means of achieving the same conditions would appear to be to allow anhydrous crystalline glucose to deliquesce in an atmosphere containing water vapour and gaseous hydrogen chloride. Thereby the molecules of glucose, which in the crystalline state are as close together as they can be, slowly move apart as water penetrates the lattice and must pass through the optimum distance for bond formation under the catalytic influence of hydrochloric acid. These conditions are realised by placing a dish containing a thin layer of crystalline anhydrous glucose in a desiccator containing concentrated hydrochloric acid to which a few drops of concentrated sulphuric acid had been added to ensure copious evolution of gas. In 3—4 days there then resulted about 17% of polymeric non-dialysable material.

Experimental.—Anhydrous glucose (50 g.) in a thin layer covering a dish 16 cm. in diameter was placed in a desiccator containing concentrated hydrochloric acid to which a few drops of concentrated sulphuric acid had been added. The crystals slowly deliquesced to a pale brown syrup. After 7 days at room temperature the syrup was dissolved in crushed ice and N-sodium hydroxide, neutralised with hydrochloric acid, and dialysed. After treatment with charcoal and filtration the colourless solution was concentrated to 25 ml. Insoluble material (fraction 1) was separated on the centrifuge, and ethanol was added to the supernatant solution to precipitate the fractions shown in the Table. All fractions were obtained as powder by trituration with ethanol, washing with ether, and drying *in vacuo* over phosphoric oxide.

Serial	Ethanol (%, v/v)	Wt. (g.)	Reducing val.	$[\alpha]_D^{20}$ (*c* 0·5 in H_2O)
1	Nil	0·36	—	Insol.
2	44·4	3·21	20·0	+106°
3	45·6	1·69	19·0	+106
4	49·4	1·81	18·8	+105
5	61·1	1·25	15·3	+104
6	78·0	0·32	10·6	+ 95
7	(from supernatant soln.)	0·16	6·0	+ 74

The reciprocal of the " reducing value " is the reducing power relative to glucose (Schaffer and Hartman, *J. Biol. Chem.*, 1921, **45**, 377) : if it is assumed that there is one reducing group per molecule these figures indicate the *number* average of the glucose units in each molecule. Paper chromatography (Jeans, Wise, and Dimler, *Analyt. Chem.*, 1951, **23**, 415) showed that only fractions 5, 6, and 7 contained saccharides mobile in the solvent system butanol–pyridine–water (6 : 4 : 3 by vol.).

All the subsequent results were obtained on fraction 2. Paper chromatography of a complete hydrolysate (2N-sulphuric acid, 100°, 4 hr., sealed tube) showed the presence of glucose only. A hydrolysate from N-sulphuric acid (100°, 5 hr.) showed 95% of the theoretical reducing power. In a partial hydrolysate (N-sulphuric acid, 0·5 hr., 100°, sealed tube) a component having the R_F value of *iso*maltose was identified by chromatography of the *N*-benzylglycosylamines (Bayly and Bourne, *Nature*, 1953, **171**, 385) and by electrophoresis in borate buffer (Foster, *Chem. and Ind.*, 1952, 1050; *J. Appl. Chem.*, 1953, **3**, 19). In each case *iso*maltose prepared from dextran was used as a reference preparation.

The infra-red absorption spectrum revealed reproducible peaks at 919, 844, 834, and 767 cm.$^{-1}$, from which it is concluded (Barker, Bourne, Stacey, and Whiffen, *J.*, 1954, 171) that the polyglucose possesses predominantly 1 : 6-α-linkages since the degree of polymerisation is greater than 5. There is no indication of 1 : 3-links or of 3 : 6-anhydro-rings. The possibility of 1 : 4-α- and a small amount of β-glucosidic linkages occurring in the polymer is not excluded.

Oxidation by 0·175M-sodium metaperiodate at room temperature evolved 0·70 mole of formic acid per anhydroglucose unit. After correction for oxidation of the terminal reducing group, 0·55 mole of formic acid is evolved per anhydroglucose unit. Thus 55—70% of the linkages between glucose units are of the 1 : 6-type. Since the evolution of formic acid falls short of the theoretical 1·0 mole per glucose unit, linkages other than the 1 : 6-link must be present.

Fraction 2 had an intrinsic viscosity in water at 37° of 0·036, the optical rotation being +106° (see Table). A partially hydrolysed dextran of similar intrinsic viscosity, 0·033, had a considerably higher optical rotation, +166°. This may be taken as a further indication that linkages other than the 1 : 6-α-link are present in this polyglucose.

The investigation is being pursued with respect to conditions and mechanism of the reaction, the condensation of other sugars, and the structure of the products.

Thanks are offered to Dr. S. A. Barker of Chemistry Department, University of Birmingham, for the infra-red and electrophoresis measurements, and to Mr. C. E. Rowe of this Unit for the periodate oxidation analysis.

MEDICAL RESEARCH COUNCIL INDUSTRIAL INJURIES & BURNS RESEARCH UNIT,
BIRMINGHAM. [*Received, June 19th*, 1954.]

Derivatives of the Coloured Compounds formed by Condensation of Furfuraldehyde with Aromatic Amines. The Compounds of Furfuraldehyde with Two Molecules of Aromatic Amines.

By J. C. McGOWAN.

[Reprint Order No. 5486.]

McGOWAN (*J.*, 1949, 777) treated the Stenhouse dye, prepared by the condensation of aniline, aniline hydrochloride, and furfuraldehyde, with aqueous sodium hydroxide and obtained a crystalline compound $C_{17}H_{16}ON_2$ which he suggested was 2(or 6)-anilino-1 : 2 : 3 : 6-tetrahydro-3-oxo-1-phenylpyridine (I or II; R = Ph). A third possibility, (III; R = Ph), has since been suggested by Dr. J. D. Kendall (personal communication) and by Dunlop and Peters (" The Furans," Reinhold Publ. Corp., New York, 1953, p. 671). A similar compound $C_{19}H_{20}ON_2$ was obtained with the Stenhouse dye from furfuraldehyde, *p*-toluidine, and *p*-toluidine hydrochloride. Rombaut and Smets (*Bull. Soc. chim. Belg.*, 1949, **58**, 421) found that 1 mol. of furfuraldehyde combined directly with 2 mols. of a number of aromatic primary amines with the elimination of 1 mol. of water. They

(I) (II) (III) (IV)

concluded, mainly on the evidence of the ultra-violet and visible-light absorption spectra, that their compounds had formula (I) or (II) but as they used neither aniline nor *p*-toluidine

direct comparison with McGowan's compound (*loc. cit.*) was not made. It has now been found that aniline and *p*-toluidine with furfuraldehyde yield compounds identical with those prepared by McGowan (*loc. cit.*) from the corresponding Stenhouse dyes and that the new method of preparation is the more convenient.

Infra-red absorption bands in the region 1590—1800 cm.$^{-1}$ are shown in the Table for relevant compounds. Jones, Williams, Whalen, and Dobriner (*J. Amer. Chem. Soc.*,

Infra-red absorption maxima (cm.$^{-1}$).

	Aniline	*p*-Toluidine
Cpd. from furfuraldehyde (in $CHCl_3$)	1710, 1639, 1597	1710, 1642, 1614
Furfurylidene deriv. (in pyridine)	1685, 1636	1693, 1639
Benzylidene deriv. (in pyridine)	1698, 1642	—

1948, **70**, 2024) studied the infra-red absorption spectra of a large number of *cyclo*hexanones and *cyclo*hexenones. In the former there was a maximum at ~1710 cm.$^{-1}$. In the latter, which had a double bond in the αβ-position to the keto-group, this maximum was shifted by about 40 cm.$^{-1}$ to lower frequencies. The carbonyl band at 1710 cm.$^{-1}$ in the aniline and *p*-toluidine compounds, therefore, suggests that the carbonyl group and double bond are not conjugated. In the furfurylidene and benzylidene derivatives, conjugation with the ethylenic double bond has caused the carbonyl group to absorb at a frequency about 20 cm.$^{-1}$ lower. Similarly, *cyclo*hexanone gave one strong band between 1600 and 1800 cm.$^{-1}$: in pyridine, at 1724 and in chloroform at 1720 cm.$^{-1}$; benzylidene*cyclo*hexanone gave two strong bands in the same region: in pyridine at 1694 and 1611, and in chloroform at 1692 and 1611 cm.$^{-1}$. These displacements are not quite as great as those found by Jones *et al.* (*loc. cit.*) but here the conjugated ethylenic bonds are exocyclic. The bands at 1636—1642 cm.$^{-1}$ suggest the presence of an ethylenic double bond. Attempts to make dibenzylidene or difurfurylidene derivatives have failed and therefore the grouping $-CH_2{\cdot}CO{\cdot}CH_2-$ is probably absent, so that the evidence now indicates fairly conclusively the structure (III).

A 3-hydroxy-2-*p*-toluidino-1-*p*-tolylpiperidine (IV; R = *p*-tolyl) (m. p. 133°) was previously prepared (McGowan, *loc. cit.*) by the reduction of 1 : 2 : 3 : 4-tetrahydro-3-oxo-2-*p*-toluidino-1-*p*-tolylpyridine (III; R = *p*-tolyl). This compound has no ethylene or carbonyl double bonds and shows no absorption bands between 1590 and 1800 cm.$^{-1}$. Since the molecule contains two asymmetric carbon atoms, diastereoisomers are possible and a second isomer (m. p. 149°) has now been isolated.

Experimental.—Microanalyses by Dr. A. F. Colson, Mr. C. E. O'Brien, and Mr. C. G. Scott. M. p.s are corrected.

Compound of aniline and furfuraldehyde, probably 2-anilino-1 : 2 : 3 : 4-tetrahydro-3-oxo-1-phenylpyridine (III; R = Ph). Aniline (91 c.c.), furfuraldehyde (41·4 c.c.), and methanol (200 c.c.) were boiled together under reflux for 2 hr., then cooled and filtered. The solid was made into a thick paste with acetone, filtered, washed with a little acetone, and recrystallised twice from ethyl alcohol [yield, 12 g.; m. p. 140° (decomp.); soluble in chloroform and pyridine] [Found: C, 77·3; H, 6·0; N, 10·3, 10·5%; *M*, 232 (ebullioscopic in C_6H_6). Calc. for $C_{17}H_{16}ON_2$: C, 77·2; H, 6·1; N, 10·6%; *M*, 264]. Acetylation (McGowan, *loc. cit.*) gave a monoacetate, m. p. 128° alone or mixed with material described previously (Found: C, 74·6; H, 5·8; N, 9·1. Calc. for $C_{19}H_{18}O_2N_2$: C, 74·5; H, 5·9; N, 9·15%).

Compound of p-toluidine and furfuraldehyde, probably 1 : 2 : 3 : 4-tetrahydro-3-oxo-2-p-toluidino-1-p-tolylpyridine (III; R = *p*-tolyl). *p*-Toluidine (107 g.), furfuraldehyde (41·4 c.c.), and methanol (200 c.c.) were refluxed for 3 hr. and then cooled. The solid was filtered off, washed with ether, and recrystallised from benzene [yield, 45·7 g.; m. p. 169° (decomp.)] [Found: C, 78·1; H, 6·6; N, 9·5%; *M*, 247 (as above). Calc. for $C_{19}H_{20}ON_2$: C, 78·0; H, 6·9; N, 9·6%; *M*, 292]. Benzoylation (McGowan, *loc. cit.*) gave a monobenzoate, m. p. and mixed m. p. 170·5° (Found: C, 78·7; H, 5·7; N, 7·2. Calc. for $C_{26}H_{24}O_2N_2$: C, 78·8; H, 6·1; N, 7·1%).

A *furfurylidene* derivative, prepared in the same way as the analogous aniline compound (McGowan, *loc. cit.*), formed yellow crystals (from 1 : 4-dioxan), m. p. 178° (decomp.) (Found: C, 78·4; H, 5·9; N, 7·2. $C_{24}H_{22}O_2N_2$ requires C, 77·8; H, 6·0; N, 7·6%).

The tetrahydro-compound was reduced as previously described (*idem, loc. cit.*). From the

mother-liquors from the recrystallisation of the compound $C_{19}H_{24}ON_2$, m. p. 133°, a small quantity of an *isomer*, m. p. 149°, was obtained (Found: C, 76·9; H, 8·1; N, 9·9%; *M*, 265. $C_{19}H_{24}ON_2$ requires C, 77·0; H, 8·2; N, 9·5%; *M*, 296). The mixed m. p. of the isomers was 120—126°.

The author thanks Mr. K. Moss for technical assistance, Mr. L. H. Cross and Mr. F. Field for infra-red spectra, and Mr. G. D. Buckley for encouragement and advice.

IMPERIAL CHEMICAL INDUSTRIES LIMITED, RESEARCH DEPARTMENT,
ALKALI DIVISION, NORTHWICH, CHESHIRE. [*Received, June 25th,* 1954.]

Miscellaneous Quinazoline Derivatives.

By K. SCHOFIELD.

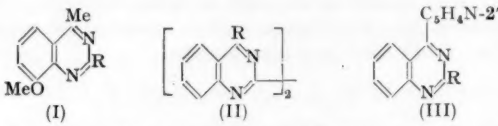
[Reprint Order No. 5488.]

THIS note describes some quinazolines of possible interest as co-ordinating reagents.

2-Acetamido- and 2-benzamido-3-methoxyacetophenone were converted by the method of Schofield, Swain, and Theobald (*J.*, 1952, 1924) into 8-methoxy-2 : 4-dimethyl- (I; R = Me) and 8-methoxy-4-methyl-2-phenyl-quinazoline (I; R = Ph), respectively. With hydriodic acid these gave the corresponding 8-hydroxyquinazolines. These compounds were inactive against *P. berghei* and *T. equiperdum*, and their bacteriostatic concentrations (mg./100 c.c. to prevent visible growth in Hedley Wright broth overnight at 37°) against three organisms are tabulated.

Quinazoline	Hæmolytic *Streptococcus*	*Staph. aureus*	*B. coli*
8-Hydroxy-2 : 4-dimethyl-	0·03	0·5	>1·0 (satd.)
8-Hydroxy-4-methyl-2-phenyl- ...	1·0	>2·0 (satd.)	>2·0 (satd.)

Oxalyl chloride reacted readily with *o*-aminoacetophenone and with *o*-amino- and 2-amino-4′-methoxy-benzophenone to give the related di-anilides, of which those from the first two amines were cyclised to give (II; R = Me) and (II; R = Ph).



2-*o*-Aminobenzoylpyridine (Ockenden and Schofield, *J.*, 1953, 3440) gave with urea 2-hydroxy-4-2′-pyridylquinazoline (III; R = OH), which was converted by phosphorus oxychloride into the chloro-compound (III; R = Cl). Unexpectedly (cf. Schofield, *J.*, 1952, 1927), catalytic reduction of the chloro-compound gave directly a poor yield of 4-2′-pyridylquinazoline (III; R = H) (unchanged by treatment with alkaline potassium ferricyanide) rather than the dihydro-derivative.

Experimental.—2-Amino-3-methoxyacetophenone (15 g.) (Alford, Irving, Marsh, and Schofield, *J.*, 1952, 3009), heated with pyridine (60 c.c.) and benzoyl chloride (15 g.) for 2 hr. at 95°, gave the anilide (22·3 g.), m. p. 108—109° (Simpson *et al.*, *J.*, 1945, 646, gave m. p. 109—110°), satisfactory for further use. Treatment of the amine (5 g.) with acetic anhydride (20 c.c.) at 95° for 2 hr., removal of the solvent at reduced pressure, and crystallisation of the residue from ethyl acetate gave 2-*acetamido*-3-*methoxyacetophenone* (4·6 g.), m. p. 128—131°, forming glistening leaflets, m. p. 133—134° (Found: C, 63·9; H, 6·3. $C_{11}H_{13}O_3N$ requires C, 63·75; H, 6·3%), from ethyl acetate.

8-*Hydroxy*-2 : 4-*dimethylquinazoline*. The amide (10·9 g.) and fused ammonium acetate (109 g.) were kept at 165—175° and treated with a rapid stream of ammonia for 3½ hr. Dissolution soon occurred. The solution was then diluted with 1·5 volumes of water, and the solid (8·6 g.) which slowly separated was collected after 2 days. (The product was noticeably soluble in cold water, and such a solution rapidly deposited heavily hydrated crystals, with evolution of heat.) Prolonged drying gave a matte solid, m. p. 81—83°, but recrystallisation

from water, followed by drying over sulphuric acid *in vacuo* for 12 hr., gave soft felted crystals of *8-methoxy-2 : 4-dimethylquinazoline dihydrate*, m. p. 62—64° (Found : C, 58·8; H, 6·8; N, 12·8. $C_{11}H_{12}ON_2,2H_2O$ requires C, 58·9; H, 7·2; N, 12·5%).

The dihydrate (2·25 g.) was refluxed for 3 hr. with hydrobromic acid (22 c.c.; *d* 1·5). Basification of the solution with aqueous ammonia gave, after some hours, a grey solid (1·2 g.), m. p. 110—115°. Recrystallisation from ethyl acetate gave fawn prisms of *8-hydroxy-2 : 4-dimethylquinazoline*, m. p. 112—113° (Found : C, 68·6; H, 5·7. $C_{10}H_{10}ON_2$ requires C, 68·95; H, 4·1%). In larger-scale experiments the discoloured product was purified by passage in ethyl acetate over alumina (on which it gave a clear yellow band, but with which prolonged contact was detrimental).

8-Hydroxy-4-methyl-2-phenylquinazoline. 2-Benzamido-3-methoxyacetophenone (22·2 g.) and fused ammonium acetate (220 g.) were treated with ammonia for 3½ hr. at 155—160°. Dilution with water gave glistening leaflets (19·9 g.), m. p. 128—130°. *8-Methoxy-4-methyl-2-phenylquinazoline* separated from methanol as yellow rods, m. p. 132—133° (Found : C, 76·4; H, 5·5. $C_{16}H_{14}ON_2$ requires C, 76·8; H, 5·6%).

The methoxy-compound (19·9 g.) was refluxed for 2 hr. with hydrobromic acid (190 c.c.; *d* 1·5). Basification of the solution with ammonia solution precipitated *8-hydroxy-4-methyl-2-phenylquinazoline* (nearly 100%) which gave leaflets (from methanol), m. p. 110—111° (Found : C, 75·75; H, 5·0. $C_{15}H_{12}ON_2$ requires C, 76·2; H, 5·1%).

Oxanilides. These were obtained in theoretical yield by treating oxalyl chloride with a 100% excess of the amine in dry benzene. From acetic acid, in which they were very sparingly soluble, *NN'-di-o-acetylphenyl-*, m. p. 270—271° (darkening) (Found : C, 66·45; H, 4·9. $C_{18}H_{16}O_4N_2$ requires C, 66·7; H, 4·9%), *NN'-di-(o-benzoylphenyl)-*, m. p. 260—261° (Found : C, 75·6; H, 4·5. $C_{28}H_{20}O_4N_2$ requires C, 75·0; H, 4·5%), and *NN'-di-(p'-methoxybenzoylphenyl)-oxalodiamide*, m. p. 269—270° (Found : C, 70·2; H, 4·6. $C_{30}H_{24}O_6N_2$ requires C, 70·85; H, 4·8%), formed needles.

Di-(4-methyl-2-quinazolinyl). The amide (3 g.) and fused ammonium acetate (90 g.) were treated with ammonia for 7 hr. at 165—175°. Addition of water precipitated the *diquinazolinyl* (2·3 g.), which formed pale yellow leaflets, m. p. 249—250° (Found : C, 75·1; H, 4·85. $C_{18}H_{14}N_4$ requires C, 75·5; H, 4·9%), from ethanol, in which it was moderately soluble.

Di-(4-phenyl-2-quinazolinyl). The anilide (0·5 g.) and fused ammonium acetate (15 g.) were treated with ammonia for 5 hr. at 160—170°. After dilution with water the product (0·39 g.; m. p. 290—291°) was collected. The *diquinazolinyl* was only very sparingly soluble in the usual solvents, and formed very pale yellow needles, m. p. 295—296° (Found : C, 81·3; H, 4·1. $C_{28}H_{18}N_4$ requires C, 81·9; H, 4·4%), from acetic acid. The insolubility of the anilide made it difficult to effect complete cyclisation on the big scale.

2-Hydroxy-4-2'-pyridylquinazoline. 2-*o*-Aminobenzoylpyridine (4·5 g.) and urea (2·25 g.) were stirred at 200—210° for 1 hr. The initial vigorous evolution of ammonia soon ended and the melt quickly solidified. The cake was pulverised and digested with alcohol, giving the product *2-hydroxy-4-2'-pyridylquinazoline* (5·1 g.), which formed cream needles, m. p. 278—280° (Found : C, 69·7; H, 3·8. $C_{13}H_9ON_3$ requires C, 69·9; H, 4·0%), from ethanol.

2-Chloro-4-2'-pyridylquinazoline. The hydroxy-compound (1 g.) and phosphorus oxychloride (6 c.c.) were refluxed for 1 hr. Decomposition of the solution with ice and sodium hydroxide, followed by ether-extraction, gave substantially pure *2-chloro-4-2'-pyridylquinazoline* (0·93 g.), needles (from methanol), m. p. 171—172° (Found : C, 64·6; H, 3·1. $C_{13}H_8N_3Cl$ requires C, 64·6; H, 3·3%).

4-2'-Pyridylquinazoline. The chloro-compound (0·5 g.) and palladium–charcoal (1·5 g., 5%) in hot methanol (50 c.c.) were shaken with hydrogen for 45 min. After removal of the catalyst and solvent the residue was treated with aqueous sodium hydroxide and extracted with ethyl acetate. The dried (Na_2SO_4) extract provided an oily solid (0·36 g.) from which was obtained with ether–light petroleum a white solid (0·15 g.), m. p. 86—87°. *4-2'-Pyridylquinazoline* separated from ligroin (b. p. 40—60°) as very pale yellow crystals, m. p. 89—90° (Found : C, 75·4; H, 4·3. $C_{13}H_9N_3$ requires C, 75·3; H, 4·4%).

I am indebted to Dr. F. Hawking of the National Institute for Medical Research for the bacteriostatic data.

WASHINGTON SINGER LABORATORIES,
PRINCE OF WALES ROAD, EXETER.

[*Received, June 25th,* 1954.]

2 : 3-*Dihydro*-1-*methyl*-7-*phenylindole.*

By J. S. Little, W. I. Taylor, and B. R. Thomas.

[Reprint Order No. 5497.]

In another connection 2 : 3-dihydro-1-methyl-7-phenylindole was required. This was prepared from *N*-methyl-2-diphenylylamine by a Fisher indole synthesis, from which some points of interest emerge.

Aqueous or aqueous-ethanolic acid hydrolysed the pyruvic acid hydrazone into its components. However in acetic acid, use of zinc chloride or boron trifluoride in ether gave the indole in good reproducible yield. We were unable to prepare the dihydroindole from 1-methyl-7-phenylindole by reduction with lithium aluminium hydride in ether or tetrahydrofuran (contrast Julian and Printy, *J. Amer. Chem. Soc.*, 1949, **71**, 3206), but did so by using zinc and hydrochloric acid.

Experimental.—Ultra-violet absorption spectra were measured in 95% EtOH.

N-2-*Diphenylyl*-N-*methylhydrazine*. *N*-Methyl-2-diphenylylamine (10 g.) in concentrated hydrochloric acid (10 ml.) was added slowly to a stirred aqueous solution of sodium nitrite (4 g.) at $<10°$. The product (11·5 g.) was filtered off and recrystallised from aqueous methanol to yield the N-*nitroso*-compound, m. p. 65—66° (Found : C, 73·4; H, 5·6; N, 12·4. $C_{13}H_{12}ON_2$ requires C, 73·6; H, 5·7; N, 13·3%). This (10 g.) in acetic acid (13 ml.) was added during 15 min. to a stirred suspension of zinc dust (3 g.) in water (20 ml.) at 5°. After 1 hr. at room temperature the whole was heated slowly to 80°, then cooled, and the bases were extracted with ether, affording after distillation the *hydrazine*, b. p. 110—113°/0·1 mm., $\lambda_{max.}$ 232 mμ (ε 13,000) (Found : C, 78·9; H, 6·7. $C_{13}H_{14}N_2$ requires C, 78·7; H, 7·1%). Its *hydrochloride* had m. p. 217—221° (from ethanol) (Found : C, 66·2; H, 6·2; N, 11·2. $C_{13}H_{15}N_2Cl$ requires C, 66·5; H, 6·4; N, 11·9%).

1-*Methyl*-7-*phenylindole*-2-*carboxylic acid*. Pyruvic acid (5 g.) and the above hydrazine (10 g.) in aqueous methanol (30 ml.) readily gave the *hydrazone*, m. p. 72° [from chloroform–light petroleum (b. p. 40—80°)], $\lambda_{max.}$ 305 mμ (ε 9000) (Found : C, 71·6; H, 6·0; N, 10·5. $C_{16}H_{16}O_2N_2$ requires C, 71·6; H, 6·0; N, 10·4%), which dissolved in concentrated hydrochloric acid giving after a few moments a crystalline precipitate of *N*-2-diphenylyl-*N*-methylhydrazine hydrochloride, m. p. 217—221°.

The hydrazone (500 mg.) was heated in acetic acid (1 ml.) with an ethereal solution of boron trifluoride (0·5 ml.) or with zinc chloride (500 mg.) at 100° for 10 min. The product, sublimed *in vacuo*, furnished after recrystallisation from ethanol 1-*methyl*-7-*phenylindole*-2-*carboxylic acid* (180 mg.), m. p. 229—232°, $\lambda_{max.}$ 296 mμ (ε 15,000) (Found : C, 76·4; H, 5·3; N, 6·1. $C_{16}H_{13}O_2N$ requires C, 76·5; H, 5·2; N, 5·6%).

2 : 3-*Dihydro*-1-*methyl*-7-*phenylindole*. The acid (80 mg.) was heated in an evacuated tube at 240° for 30 min. The crude oily 1-methyl-7-phenylindole was characterised as its dark red *picrate*, m. p. 107—108° (from ethanol) (Found : C, 57·3; H, 3·8; N, 13·0. $C_{21}H_{16}O_7N_4$ requires C, 57·8; H, 3·7; N, 12·8%). The picrate (100 mg.) was decomposed on an alumina column, affording oily 1-methyl-7-phenylindole (54 mg.), $\lambda_{max.}$ 293 mμ (ε 6200), which was refluxed for 1 hr. with zinc (2 g.) and concentrated hydrochloric acid (10 ml.). The solution was made alkaline and extracted with ether. The extract was dried, filtered through alumina, and concentrated, and the product sublimed to give the colourless oily dihydroindole (40 mg.), $\lambda_{max.}$ 310 mμ (ε 7000), characterised as its *picrate*, m. p. 180—181° (Found : C, 57·5; H, 3·9; N, 13·2. $C_{21}H_{18}O_7N_4$ requires C, 57·5; H, 4·2; N, 12·8%).

We are indebted to the National Research Council of Canada for a grant and an N.R.C. Postdoctorate Fellowship to one of us (B. R. T.).

Chemical Laboratories,
University of New Brunswick.

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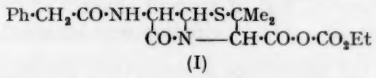
Benzylpenicillinic Thioanhydride.

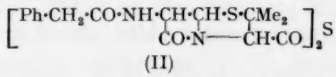
By R. M. Evans and A. B. A. Jansen.

[Reprint Order No. 5502.]

The interaction of benzylpenicillinic ethoxyformic anhydride (I) with amines, alcohols, and thiols to form, respectively, amides, esters, and thioesters of penicillin has been described by Johnson (*J. Amer. Chem. Soc.*, 1953, **75**, 3636) and by Barnden, Evans, Hamlet, Hems, Jansen, Trevett, and Webb (*J.*, 1953, 3733). We have now examined the reaction of the anhydride with hydrogen sulphide. Cronyn and Jui (*J. Amer. Chem. Soc.*, 1952, **74**, 4726) and Sheehan and Johnson (*ibid.*, p. 4727) have shown that acylamino-acids may be converted into the corresponding thio-acids by treating their ethoxyformic anhydrides in methylene chloride at $-20°$ with hydrogen sulphide in the presence of a molar proportion of triethylamine. Under these conditions (I) gave only intractable products, but benzylpenicillinic thioanhydride (II) was obtained as a crystalline solid in 69% yield when much less triethylamine was employed.



(I)



(II)

For the preparation of the thioanhydride the progress of the reaction was best followed polarimetrically, the product being worked up when the rotation reached a maximum. When the reaction time was prolonged beyond this, there were formed neutral and acidic substances devoid of anti-bacterial activity and having a relatively low specific rotation. It is therefore probable that fission of the β-lactam ring had occurred. The velocity of the reaction of benzylpenicillinic ethoxyformic anhydride with hydrogen sulphide is increased markedly by increasing quantities of base and is apparently affected also by impurities, whose nature is at present unknown.

The thioanhydride was stable for several months in a stoppered bottle as the dry crystalline solid, but deteriorated more rapidly in solution in organic solvents or in suspension in water, and it reacted with *cyclo*hexylamine to give penicillin *cyclo*hexylamide in 42% yield. On plate bioassay against *Staphylococcus aureus* the thioanhydride showed an activity of 1500 i.u./mg. which was first thought to be due solely to sodium penicillin formed by hydrolysis of the thioanhydride in the buffer solution (quantitative hydrolysis would give 1760 i.u./mg.), but an anomalously high activity, 4000 i.u./mg., was observed when *Bacillus subtilis* was the test organism and indicated the presence of another active substance. Further examination was kindly undertaken by Dr. P. Muggleton and his staff, who found that the activity was normal against *Sarcina lutea*, *Coryne bacterium diphtheriae*, *Streptococcus* β-*haemolyticus*, and *Clostridium welchii*. Evaluation of the compound, whether administered orally or by injection, showed it to be of little use therapeutically.

Experimental.—Benzylpenicillinic thioanhydride. Ethyl chloroformate (6 c.c.) was added to a solution of triethylammonium benzylpenicillinate (26·1 g.) in chloroform (120 c.c.); after 10 min., the mixture was treated with a solution (90 c.c.; 0·7M; estimated iodometrically) of hydrogen sulphide in chloroform, together with triethylamine (8 drops). After 1 hr. at room temperature the optical roatation of the solution, observed in a 1-dm. tube, had increased from $+18·7°$ to $+28·1°$. The solution was then washed successively with water, citric acid solution, disodium hydrogen phosphate solution, and water, then dried (Na_2SO_4), and evaporated *in vacuo*. The residual resin was crystallised from ethyl acetate–*iso*propyl ether, affording colourless prisms (13·75 g.), m. p. 130°, $[\alpha]_D^{20} + 384°$ (*c*, 1·0 in $CHCl_3$) (Found: C, 57·85; H, 5·45; N, 8·8; S, 13·9. $C_{22}H_{34}O_6N_4S_3$ requires C, 57·65; H, 5·1; N, 8·4; S, 14·4%).

Reaction of the thioanhydride with cyclo*hexylamine.* *cyclo*Hexylamine (0·24 c.c.) was added to a solution of the thioanhydride (0·67 g.) in chloroform (10 c.c.) and, after ½ hr., the solution was washed in turn with water, dilute hydrochloric acid, disodium hydrogen phosphate solution, and water. Evaporation of the dried solution afforded a crystalline residue (0·35 g.) which, after recrystallisation from ethyl acetate, had m. p. 197—198°, not depressed on admixture with authentic benzylpenicillin *cyclo*hexylamide.

Glaxo Laboratories, Ltd., Greenford, Middlesex. [*Received, June 29th*, 1954.]

The Oxidation of Americium to the Sexavalent State.

By M. Ward and G. A. Welch.

[Reprint Order No. 5510.]

Asprey, Stephanou, and Penneman (*J. Amer. Chem. Soc.*, 1950, **72**, 1425; 1951, **73**, 5715) state that tervalent americium is oxidised completely in 10 minutes to the sexavalent state in 0·2M-nitric acid at 85° by ammonium persulphate; also by the addition of solid argentic oxide to a dilute perchloric acid solution of americium.

Oxidation of americium in tracer amounts to its sexavalent state was achieved partially by addition of iodic acid to an americium solution in 0·2M-nitric acid (approximately 30% oxidised), and also by the passage of ozone (5% ozone at 3 ml./min.) into an americium solution in 0·2M-nitric acid for 1 hr. [20% americium(VI) obtained].

At room temperature the addition of ammonium persulphate to americium solutions, at varying acid strengths, induced no oxidation at all. At 85—90°, the reaction in 0·2M-nitric acid produced only up to 80% americium(VI), but, if a small amount of silver (as silver nitrate) was also added, almost complete (98—99%) oxidation was achieved.

Experimental.—In most of the experiments the percentage of sexavalent americium was followed by making use of the fact that, unlike tervalent americium, it is not coprecipitated on lanthanum fluoride. In a typical experiment in which 99% oxidation was obtained, the americium solution (containing 2×10^5 α d.p.m.) was pipetted into a 3-ml. centrifuge tube, and made 0·3M with respect to nitric acid, the final volume being 1 ml. One drop of 10% silver nitrate and 8 drops of 5% ammonium persulphate solution were added and the mixture was heated in boiling water for 4 min. A further 8 drops of 5% ammonium persulphate were added and the tube heated for a further 2 min. Lanthanum carrier (0·5 mg.) was added as nitrate solution and the unoxidised americium co-precipitated on lanthanum fluoride by the addition of ammonium fluoride solution. The ammonium fluoride was treated with argentic nitrate just before use to prevent any reduction of the americium by impurities in the fluoride. The lanthanum fluoride was centrifuged out, then washed twice, and its americium content determined by alpha-counting.

Thanks are offered to Dr. Milsted of A.E.R.E. for supplying the americium and to the Managing Director, Department of Atomic Energy (Industrial Group), for permission to publish this note.

Chemical Services Department, Department of Atomic Energy (Industrial Group), Windscale Works, Cumberland. [*Received, July 1st*, 1954.]

The Tuberculostatic Activity of Pyridine-acid Hydrazides.

By A. R. Katritzky.

[Reprint Order No. 5539.]

The outstanding activity, as tuberculostatic agent, of *iso*nicotinic hydrazide (Fox and Gibas, *J. Org. Chem.*, 1952, **17**, 1653) is not an isolated instance among pyridine-acid hydrazides, since picolinic hydrazide is very potent, although too toxic for clinical use (*idem, loc. cit.*). In view of the availability of the corresponding esters (in connection with another investigation), it was of interest to prepare and test biologically 4-pyridylacethydrazide, β-4-pyridylpropionhydrazide, and β-4-pyridylacrylhydrazide. Imperial Chemical Industries Limited, Dyestuffs Division, who kindly undertook the testing, report that the compounds are inactive in tubercular-infected mice. It thus appears that direct attachment of the $CO{\cdot}NH{\cdot}NH_2$ group to the pyridine nucleus is necessary for activity.

4-Pyridylacethydrazide separated from ethyl acetate with 0·22 molecule of solvent of crystallisation; β-4-pyridylpropionhydrazide from the same solvent contained 0·23 and from chloroform 0·22 molecule of solvent. These may be clathrate compounds (Powell, *J.*, 1948, 61), perhaps with an ideal solvent–solute ratio of 1 : 4.

Experimental.—*4-Pyridylacethydrazide.* Ethyl 4-pyridylacetate (3 g.) and hydrazine hydrate (100%; 1·5 c.c.) were heated on the water-bath for 2 hr. At first the *hydrazide* separated from ethyl acetate in fine needles turning to stout needles, m. p. 51—54°; in later recrystallisations fine needles turning to plates were obtained, the m. p. of which varied 50° to 120° with the rate of heating. At 120° its loss in weight was 11·4% corresponding to 0·22 mol. of solvent (Found in the residue: C, 55·6; H, 6·0. $C_7H_9ON_3$ requires C, 55·6; H, 6·0%).

β-4-*Pyridylpropionhydrazide*, prepared as above, separated from chloroform in colourless solvated needles, m. p. 55—65°. At 120° its loss in weight was 13·7% corresponding to 0·22 mol. of solvent (Found in the residue: C, 58·1; H, 6·9. $C_8H_{11}ON_3$ requires C, 58·2; H, 6·7%). The compound was also obtained in solvated needles, m. p. 64—65°, from ethyl acetate, which lost 10·9% in weight, corresponding to 0·23 mol. of solvent (Found in the residue: C, 58·3; H, 6·9%). The *benzylidene* derivative, prepared in boiling ethanol, separated from amyl alcohol in colourless prisms, m. p. 186—187° (Found: C, 71·3; H, 6·1. $C_{15}H_{15}ON_3$ requires C, 71·1; H, 5·9%).

β-4-Pyridylacrylhydrazide, prepared as above, did not crystallise. It formed an ill-defined yellow *dipicrate*, m. p. 80—90° (decomp.) (Found: C, 38·6; H, 2·8. $C_{20}H_{15}O_{15}N_9$ requires C, 38·6; H, 2·4%).

The author is indebted to Professor Sir Robert Robinson, O.M., F.R.S., for his interest. Grateful acknowledgment is also made to the Ministry of Education for an F.E.T.S. maintenance grant.

THE DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, July 9th,* 1954.]

The Preparation of 2 : 3-*Diaminopyridine.*

By C. L. LEESE and H. N. RYDON.

[Reprint Order No. 5555.]

THE simplest route to 2 : 3-diaminopyridine from the commercially available 2-aminopyridine, *viz.*, nitration, separation of the 3- and the 5-nitro-compound (Tschitschibabin, *J. Russ. Phys. Chem. Soc.*, 1914, **46**, 1236; Caldwell and Kornfeld, *J. Amer. Chem. Soc.*, 1942, **64**, 1695), and reduction of the former (Tschitschibabin and Kirssanov, *Ber.*, 1927, **60**, 771; Petrow and Saper, *J.*, 1948, 1389), is unsuitable for the preparation of any considerable quantity of the diamine owing to the small proportion of 3-nitro-compound formed and the large bulk of liquid which has to be handled in its separation.

The obvious alternative route involves halogenation of 2-aminopyridine in the 5-position (Tschitschibabin and Egorov, *J. Russ. Phys. Chem. Soc.*, 1928, **66**, 683; Case, *J. Amer. Chem. Soc.*, 1946, **68**, 2574), nitration in the 3-position (Petrow and Saper, *loc. cit.*; Vaughan, Krapcho, and English, *J. Amer. Chem. Soc.*, 1949, **71**, 1885), reduction of the 3-nitro-group, and removal of the 5-halogeno-group by hydrogenolysis. Ziegler (*ibid.*, p. 1891) brought about the last two stages in one operation, obtaining 2 : 3-diaminopyridine in 63% yield from 2-amino-5-chloro-3-nitropyridine by treatment with Raney nickel alloy in sodium hydroxide solution, but we were unable to obtain satisfactory yields by this method; a similar reaction with 2-amino-5-bromo-3-nitropyridine gave a 56% yield but the 2 : 3-diaminopyridine prepared in this way darkened rapidly on storage.

A satisfactory method, which has given consistent yields (18% overall from 2-aminopyridine) of material of good quality, is described below. 2-Aminopyridine is brominated by a modification of Case's method (*loc. cit.*), the product is then nitrated and reduced (cf. Petrow and Saper, *loc. cit.*), and the resulting 2 : 3-diamino-5-bromopyridine hydrogenolysed over palladised strontium carbonate in aqueous alkali.

Experimental.—*2-Amino-5-bromopyridine.* Bromine (435 g.) was added with stirring to a cooled solution of 2-aminopyridine (255 g.) in ethanol (1·5 l.). The crystalline precipitate was collected, washed with ethanol, and dissolved in water (400 ml.); basification precipitated the crude bromo-compound which was collected by filtration, washed, dried, freed from the accompanying 3 : 5-dibromo-compound by two extractions with warm light petroleum (b. p. 60—80°), and recrystallised from benzene; it had m. p. 137° (lit., m. p. 137°), the yield being 207 g. (44%).

2 : 3-*Diamino-pyridine.* (*a*) 2-Amino-5-bromopyridine was nitrated in 60% yield and the resulting 2-amino-5-bromo-3-nitropyridine reduced to 2 : 3-diamino-5-bromopyridine in 80% yield by Petrow and Saper's procedures (*loc. cit.*). The bromo-diamine (20 g.) was suspended in N-sodium hydroxide solution (100 ml.) and shaken with hydrogen in the presence of 5% palladised strontium carbonate (0·5 g.). When the uptake of hydrogen was complete, the catalyst was removed and the filtrate saturated with potassium carbonate (105 g.) and continuously extracted with ether for 12 hr. After removal of the ether from the dried extract, the residue was recrystallised (charcoal) from benzene (75 ml.). The yield of 2 : 3-diamino-pyridine, colourless needles, m. p. 116° (Tschitschibabin and Kirssanov, *loc. cit.*, give m. p. 112—113°; Petrow and Saper, *loc. cit.*, give m. p. 118·5—119·5°), was 9·9 g. (86%).

(*b*) 2-Amino-5-bromo-3-nitropyridine (3·2 g.) was suspended in 10% sodium hydroxide solution (75 ml.) and ethanol (10 ml.), and the mixture heated to 60°. Raney nickel alloy (7·5 g.) was added to the stirred mixture during 30 min., the temperature being kept at 60—65°; more ethanol (10 ml.), followed by more alloy (1 g.) was then added, the temperature being raised to 80°. The mixture was then cooled and filtered and the filtrate saturated with potassium carbonate and continuously extracted with ether for 12 hr. after addition of sodium dithionite (1 g.). Evaporation of the dried extract and crystallisation from benzene gave the diamine (0·9 g., 56%) as grey needles, m. p. 111°.

We thank the Medical Research Council for a studentship awarded to one of us (C. L. L.).

ORGANIC CHEMISTRY DEPARTMENT,
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LONDON, S.W.7.

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Pyrindane (2 : 3-cyclo*Pentenopyridine*) *as a Coal-tar Base.*

By P. ARNALL.

[Reprint Order No. 5611.]

NISBET and PRYDE (*Nature*, 1951, **167**, 862; 1951, **168**, 832) have reported the occurrence of 2 : 3 : 5 : 6- and 2 : 3 : 4 : 6-tetramethylpyridine in fractions of coal-tar bases boiling near 200°/760 mm. During the examination in these laboratories of crude bases extracted from the light creosote fraction of a predominantly vertical-retort tar, in addition to these two, 2 : 3-*cyclo*pentenopyridine has been isolated from a fraction of similar boiling range. This compound, though known as a constituent of shale-oil bases (Eguchi, *Bull. Chem. Soc. Japan*, 1928, **3**, 239), had not previously been identified in coal-tar bases although the corresponding hydrocarbon series (indane; Kramer and Spilker, *Ber.*, 1896, **29**, 552) and phenols (4- and 5-hydroxyindane; Kruber and Schmieden, *Ber.*, 1939, **72**, 653; Kruber and Marx, *Ber.*, 1940, **73**, 1175) are well known.

Experimental.—A bases fraction of b. p. 198—204° was dissolved in hydrochloric acid and extracted with chloroform (Perrin and Bailey, *J. Amer. Chem. Soc.*, 1933, **55**, 4136). The " aromatic " bases whose hydrochlorides were insoluble in chloroform were recovered, primary amines were removed by acetylation, and the residual bases were stirred with excess of concentrated urea solution. Milner (B.P. 584,148) and Riethoff (U.S.P. 2,295,606, 2,376,008) showed that complexes were formed between 2 : 3- and 2 : 6-lutidine and urea. This was expected also for simple pyridine homologues with 2 : 3- and 2 : 6-methyl groups. The precipitate formed was filtered off and decomposed by boiling water. Bases recovered from the filtrate and from the precipitate were each distilled through a fractionating column of approx. 70 plates efficiency. Each of these bases contained a base of high refractive index which could not be an unacetylated primary amine since these were shown to be absent. Selected fractions from each distillation were blended and treated stepwise with picric acid. The fractions from the urea-reacting bases yielded 2 : 3 : 5 : 6-tetramethylpyridine picrate, m. p. 175—176°, and a picrate of m. p. 180·5—182° in the ratio of 1 : 3½ together with a quantity of uncrystallisable syrup. Other fractions yielded 2 : 3 : 4 : 6-tetramethylpyridine picrate, m. p. 123·5—124°. The fractions from the bases which did not react with urea yielded 2 : 3 : 5 : 6-tetramethyl-pyridine picrate and a picrate of m. p. 181—182° in the ratio of 1 : 1½, and smaller amounts of unidentified picrates. The picrates of m. p. ~182° were identical (mixed m. p.) and on recrystallisation from glacial acetic acid the total product had m. p. 181—182°.

This picrate was decomposed by addition of potassium carbonate solution and distillation in steam, the distillate was dehydrated, and the base distilled (199·3—199·4°/760 mm.). Eguchi (*loc. cit.*) gives for 2 : 3-*cyclo*pentenopyridine b. p. 199·8°/761 mm., and 181° for the m. p. of the picrate. The other properties of the base, as follows, confirm the identity (in parentheses are given values by Prelog and Szpilfogel, *Helv. Chim. Acta*, 1945, **28**, 1684); d_{20}^{20} 1·0363 (d_4^{20} 1·0359), n_D^{20} 1·5444 (1·54446), styphnate m. p. 177·5° (decomp.) [(178—179° (decomp.)], picrolonate m. p. 239° (decomp.) [(235—236° (decomp.)]. A sample of the picrate synthesised by Prelog and Szpilfogel's method (*loc. cit.*) was identical (mixed m. p.) with that from our base. The infra-red spectra were also identical; they were determined by Mr. D. D. Shrewsbury using a prototype model double-beam infra-red spectrometer on loan from Messrs. Unicam Instruments Limited: the principal bands (cm.$^{-1}$) were at 722 m, 741 m, 789 s, 851 w, ~885 w, 907 w, ~943 w, ~978 w, 1000 w, 1035 m, 1090 s, 1153 m, 1186 w, 1215 m, 1263 w, 1313 m, 1389 w (shoulder), 1420 s, 1441 s, 1467 m, 1592 s, 1721 m, ~1910 w, and 1929 w (s = 71—100%, m = 31—70%, w = ⩾30%).*

In this work 2 : 3 : 4 : 6-tetramethylpyridine was found exclusively in the urea-reacting bases as was expected; 2 : 3 : 5 : 6-tetramethylpyridine and pyrindane were found both in the urea complex and in the liquor. 2 : 3 : 4 : 6-Tetramethylpyridine forms a solid complex with urea while, contrary to expectation 2 : 3 : 5 : 6-tetramethylpyridine does not. 2 : 3-*cyclo*-Pentenopyridine forms an unstable complex and the presence of the last two compounds in both precipitate and liquor is attributed to physical distribution between the solid and the liquid phase.

The author thanks Dr. E. R. Wallsgrove for helpful discussion, Miss J. M. Moon for assistance in the experimental work, Professor H. B. Nisbet for a sample of 2 : 3 : 4 : 6-tetramethylpyridine, and the Directors of The Midland Tar Distillers Ltd. for permission to publish this note.

THE MIDLAND TAR DISTILLERS LIMITED, RESEARCH DEPARTMENT,
FOUR ASHES, NEAR WOLVERHAMPTON. [*Received, July* 31*st*, 1954.]

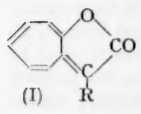
A Reaction of 2-*Chloro*cyclo*heptatrienone.*

By J. W. COOK, J. D. LOUDON, and R. K. RAZDAN.

[Reprint Order No. 5624.]

CONDENSATION of 2-chloro*cyclo*heptatrienone with ethyl acetonedicarboxylate afforded (I; R = CO·CH_2·CO_2Et) which by acid hydrolysis yielded (I; R = COMe) apparently identical with the compound (m. p. 204—205°) obtained by Nozoe, Seto, and Matsumura (*Proc. Jap. Acad.*, 1952, **28**, 483; Seto, *Sci. Rep. Tôhoku Univ.*, 1953, **37**, 367) through a similar condensation using ethyl acetoacetate.

Experimental.—2-Chloro*cyclo*heptatrienone (0·9 g.) was added to the sodio-derivative of ethyl acetonedicarboxylate—from the ester (1·44 g.) and atomised sodium (0·16 g.)—in ether (50 c.c.), and the deep-red solution, after 18 hr. at room temperature, was heated under reflux for 1 hr., cooled, washed with water and concentrated, affording *γ-ethoxycarbonyl-α-2-hydroxy*cyclo*heptatrienylidene-β-oxobutyrolactone* as yellow plates, m. p. 126° (from ethanol) (Found: C, 64·5; H, 4·5; double bonds, 3·85, by micro-hydrogenation. $C_{14}H_{12}O_5$ requires C, 64·6; H, 4·6%). Light absorption in ethanol: $\lambda_{max.}$, 4225, 2750, 2500, 2250 Å; log ε 4·40, 4·32, 4·24, 4·41. The compound gave a green-brown colour with ferric chloride in ethanol; when it (0·1 g.) was heated (2 hr.) with concentrated hydrochloric acid (5 c.c.) and water (20 c.c.), recovery in chloroform afforded α-2-hydroxy*cyclo*heptatrienylidene-β-oxobutyrolactone (I; R = CO·CH_3) as yellow needles, m. p. 210° (from ethanol) (Found: C, 70·1; H, 4·2; double bonds, 4·2, by micro-hydrogenation. Calc. for $C_{11}H_8O_3$: C, 70·2; H, 4·25%). The latter had light absorption in ethanol: $\lambda_{max.}$, 4200, 2725, 2475, 2225 Å; log ε 4·38, 4·32, 4·26, 4·42.



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THE UNIVERSITY OF GLASGOW. [*Received, August 6th*, 1954.]

* A copy of the spectrum has been deposited with the Chemical Society. Photocopies (price 3*s.* 0*d.* each) may be obtained from the General Secretary on application quoting C.S. no. 140.

The Hudson Memorial Lecture.

CLAUDE SILBERT HUDSON.

DELIVERED BEFORE THE CHEMICAL SOCIETY AT BURLINGTON HOUSE ON JUNE 3RD, 1954.

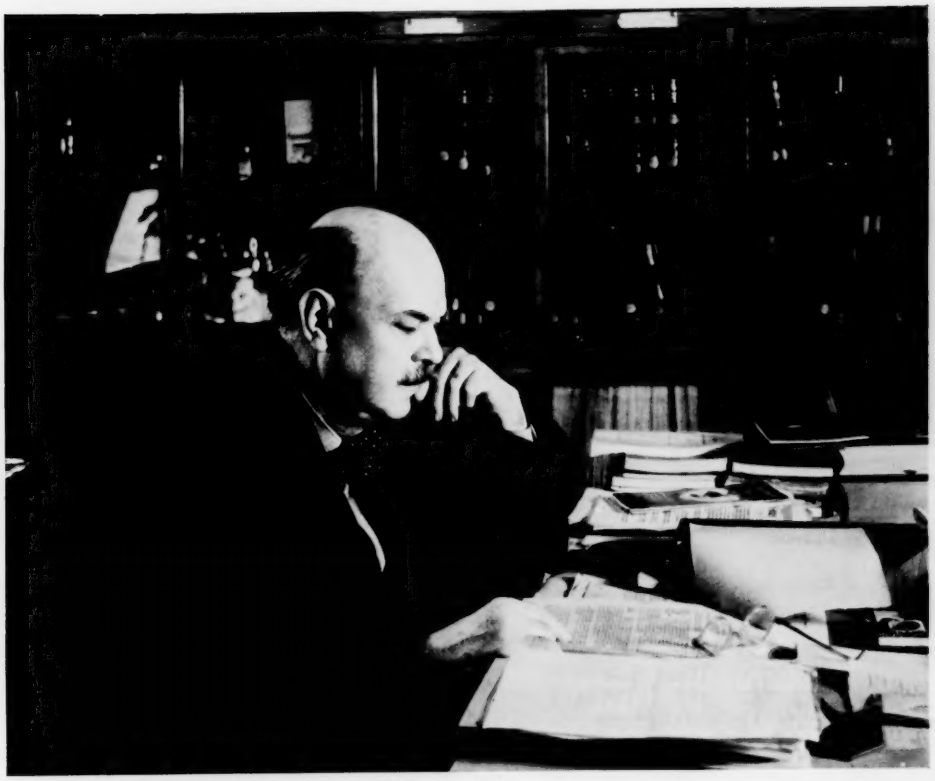
By E. L. HIRST, D.Sc., LL.D., F.R.S.

CLAUDE SILBERT HUDSON (1881—1952) will take his place along with Sir James Irvine (1877—1952) and Sir Norman Haworth (1883—1950) as one of the pioneers of modern carbohydrate chemistry. For more than 40 years he was regarded as a leading authority in a field which had become transformed out of all recognition since the time when in 1901 he began his classical investigations into the mutarotation of lactose. Indeed, for so long had Hudson and his work been known to a wide circle of friends and colleagues that he might almost be said to have achieved the rare distinction of becoming a legendary figure during his own lifetime. Quite apart from his work Hudson's rich colourful personality contributed to this and to those whose privilege it was to know him his warm friendliness, his keen interest and original mind, and his extraordinary patience and skill in laboratory work rendered him unique and evoked from all both respect and regard. In the foreword to the volumes containing his collected papers which were published in his honour in 1946, Hudson wrote that at first he resisted a request for an autobiographical notice but was later persuaded by H. O. L. Fischer that future readers might " desire to know what sort of a person this man Hudson was and how it came about that he carried out these chemical researches." This is certainly true and in his case it is singularly difficult to separate his personality from the record of his scientific achievements, so before any attempt can be made to assess the latter it is essential to consider briefly something of his history and upbringing.

The story is one of quite unusual interest. Claude Silbert Hudson was born in Atlanta, Georgia, on January 26th, 1881, the second child of William James Hudson (1851—1931) and his wife Maude Celestia Wilson (1854—1932). Through his father he could trace his ancestry back to Joseph Gregg, a member of a Scottish family which migrated to Londonderry, Ulster, in the late 17th century and from there to South Carolina about 1752. In 1812 Joseph Gregg's daughter Margaret married Robert Hudson, a wealthy plantation owner in Williamsburg County and their eldest son was C. S. Hudson's grandfather. His mother's ancestry was a mixture of English, Scots, and Huguenot French, and on this side both his grandfather and greatgrandfather were physicians. The early portion of William Hudson's life had been spent in South Carolina, but in the troubled period after the Civil War he left his father's estate and entered business in Georgia. Soon after the birth of Claude Silbert Hudson his parents moved to Greenville, Alabama, and then, when he was three years old, to Mobile where his father was occupied in the fertiliser business, ultimately becoming President of the Mobile Fertilizer Company.

It was therefore in this pleasantly situated and small but active southern town with its unusual community of families with cultures stemming from a wide group of European countries that C. S. Hudson passed the impressionable years of his boyhood. In later times he recorded his memories of those early days, the festivities and processions, the quiet dignified home with its trees and gardens, the pleasant outdoor life of swimming, fishing, and sailing which could be enjoyed in the warm climate. He recalled too encouragement he received from his parents during his school days at the Barton Academy in Mobile and at the University Military School supervised by Julius T. Wright, a man who exercised a deep influence over Hudson in his dual capacity of headmaster and Sunday School Teacher at Government St. Presbyterian Church. During this period Hudson came to know the Rev. A. C. Harte, secretary of the Mobile Y.M.C.A. and like J. T. Wright a man of high culture and saintliness of character.

C. S. Hudson as a boy had early displayed a seriousness of outlook which was manifested in his interest in various church activities. It is not altogether surprising therefore to find that when he was ready to enter college at the early age of 16 it was with the fixed intention of training for the Presbyterian Ministry. So in 1897 he entered Princeton where he knew nobody and as a southerner found the northern speech and customs of his classmates very strange. Perhaps even stranger still was the fact that here he was established in Princeton studying to enter the Presbyterian ministry but enrolled nevertheless in the course leading to the B.Sc. degree. His idea was, apparently, that he would prepare for his prospective duties by learning as much science as



Claude S. Hudson

[*To face p.* 4012.

possible and during his freshman year he attended Professor L. W. McCay's chemistry class where he was profoundly impressed by the brilliant lectures and the excellence of the demonstrations. So much was this the case that when he returned to Princeton in the autumn of 1898, after a summer spent as assistant to the Rev. A. C. Harte in Y.M.C.A. work for the second Alabama Regiment mobilised for service in the Spanish American war, he came to realise that he possessed but little aptitude for ministerial work and decided to aim for a scientific career. The interest he found in the courses in physics (Professor E. H. Loomis), astronomy (Professor C. A. Young), geology (Professor W. B. Scott), and mathematics (Professor C. G. Rockwood, Jr.) confirmed this decision and after a highly successful 4 years at Princeton he graduated in 1901.

At this period he was much worried about his future. He wished to continue in academic work but his father could no longer support him and he had made arrangements to join his former headmaster J. T. Wright as an assistant teacher at the University Military School at Mobile when, quite unexpectedly, the whole course of his career was changed. It so happened that in 1901 a Princeton Fellowship in experimental science was due to be awarded to a chemistry graduate and in May 1901 it was offered to Hudson. Wright, considerate and friendly as always, released Hudson from his engagement and in the autumn of that year he was fairly launched on a career in chemistry. His leanings were towards physical chemistry which was then taught by Professor Loomis in the Physics Department. Before the new Fellow had decided upon a problem for investigation Professor Magie of the Physics Department asked Hudson to crystallise a sample of lactose which was needed for some specific-heat measurements—a fateful request the consequences of which are best told in Hudson's own words.

"During a measurement of the rotation of the sugar as a control of purity, I noticed its mutarotation, a phenomenon of which I had never heard, and asked Dr. Magie for its explanation. He found Erdman's measurements of it in the *Berichte* (1880, **13**, 2180), but none of the current general treatises gave any real explanation of mutarotation. I promptly requested that my research problem be a physico-chemical study of the mutarotation of milk sugar. The result from my request was an unexpected one. Dr. Magie consulted Professor Neher, who told him that it would be unfair to a student to let him select a subject in sugar chemistry because the chemistry of sugars had recently been thoroughly explored by Emil Fischer. But Dr. Magie over-ruled Neher when the latter could not show that Fischer had disclosed the cause of mutarotation; the final decision was that the Chemistry Department would be relieved of all responsibility toward me beyond the supplying of a laboratory bench and chemicals, and that during my research on the mutarotation of milk sugar I would report to Dr. Magie. This decision delighted me and I went ahead with enthusiasm; my first scientific paper was on the forms of milk sugar, published near the end of the fellowship year, at the age of twenty-one."

In this unexpected way and almost accidentally, Hudson began his long series of investigations in the sugar group. The work on lactose brought him the M.Sc. degree in 1902 and he now decided to gain further experience by postgraduate study in Germany. The state of the family finances at this time was such that it appeared to be just possible for him to stay in Europe for 3 years. It was arranged that he should go to Nernst's laboratory at Göttingen, where he continued his investigations on the mutarotation of milk sugar and had numerous discussions with Tollens in the laboratory of Agricultural Chemistry. He learned much but records that he was teacher as well as pupil in that one of his very successful activities was to interest Nernst in the game of poker.

Once again, however, difficulties arose which threatened Hudson's whole career. Financial troubles at home made it imperative for him to give up the idea of 3 years' study in Europe and to return to the U.S.A. at the end of one session. Characteristically he made the utmost use of the time he had. Before leaving Göttingen he spent some weeks in Tammann's laboratory testing experimentally the idea which had come to him while reading Landolt's book on optical activity, that the temperature–solubility curve for the nicotine–water system would take the form of a closed ring. He spent the summer semester in van't Hoff's laboratory in Charlottenberg working on the aqueous vapour pressure of lactose monohydrate, receiving much inspiration from personal contact with so striking a character as van't Hoff. Before returning to the States he had an opportunity to meet Emil Fischer whom he always regarded as the greatest organic chemist of his age.

At the International Chemical Congress in Berlin in the summer of 1903 Hudson met A. A. Noyes who offered him a place in the new research laboratory for physical chemistry at the Massachusetts Institute of Technology in Boston. Here work on the inter-relationship between the various forms of lactose was continued and proposals were made for an extension of the programme to include mannose. Attempts to secure funds for this work were unsuccessful and

Hudson, greatly discouraged, applied unsuccessfully for a vacant professorship in one of the colleges in the State of Washington. He then returned to Princeton for a year as an instructor in physics, following this in 1905 by taking a similar post in the University of Illinois. These positions were nevertheless only stop-gaps since it was by now abundantly clear that Hudson's talents lay in the chemical field rather than in physics. His efforts to secure a teaching or research post in chemistry met with nothing but failure and almost in despair he asked his father to take him into the family mining business at Twomey. He was prevailed upon to wait a little longer before taking the final decision and shortly afterwards the crisis passed when in 1907 he was unexpectedly offered the post of Assistant Physicist in the Technologic Branch of the U.S. Geological Survey.

The short period in Germany had not permitted him to take the Ph.D. degree which was the passport to so many chemical posts, but this handicap was removed when he gained, *magna cum laude*, the Ph.D. of Princeton in 1907. It is interesting to note that the diploma was signed by Woodrow Wilson who was then President of Princeton. A striking illustration of Hudson's single-minded devotion to research occurred during the short visit he made to his old University to obtain the degree. He took the opportunity to spend a few days in experimental work on sugar chemistry in Professor Hulett's laboratory, and in the course of this he measured the rate of mutarotation of glucose at differing pH values and put forward the equation for the reaction which came to be generally accepted.

Hudson was now nearly 27. He knew the work he wanted to undertake but he still had no settled post in which he could pursue it. The work of the Technologic Branch served only to divert his attention from his true field and in any case its activities were soon curtailed and he moved to a post in the New York Testing Laboratory at the plant of the Barber Asphalt Company, New Jersey. The year 1908 marked the beginning of a new era in Hudson's research activities but once again the circumstances were so unusual that they are well worth recounting as illustrating both the personality of Hudson and the extraordinary series of vicissitudes which had to be surmounted before his real work could be begun. In March 1908 he became Chemist Aid in the Bureau of Chemistry at Washington where his duties were to assist Frederick Weber in routine analyses. These were so well organised by Hudson that, his work completed, he was allowed to spend two hours a day in the library. His reading, chiefly it is to be noted in sugar chemistry, was to such good effect that it led in a short time to his paper of January 1910 on "The Significance of Certain Numerical Relations in the Sugar Group." The suspension of the analytical work owing to political difficulties enabled Hudson to give his whole attention to research for the time being and, still interested in mutarotation, he sought and obtained permission to study the rotational changes observable during the hydrolysis of sucrose by invertase. This was the beginning of a notable series of investigations on the enzyme invertase carried out over a period of years, many of them in collaboration with C. B. Purves. Hudson's position was now secure. He soon became head of a section of Physical Chemistry in the Bureau and was given leave of absence for the session 1911 to return to Princeton as Acting Professor of Physical Chemistry. On his return to the Bureau of Chemistry in 1912 he was given charge of the newly established Carbohydrate Laboratory. He now had the opportunities he had so long wished for and he took the fullest advantage of them publishing year by year a large number of papers on carbohydrate chemistry characterised throughout by the precision and accuracy of the experimental work and the clarity of the writing and argument.

By 1914 Hudson's work had earned for him an international reputation as an authority on rare sugars and an interesting side-light on this is to be found in the request made to him at the beginning of the 1914—18 war for details of the methods of preparation he had devised for several sugars and sugar derivatives which were urgently required by the British Health services.

It was not long, however, before Hudson himself became involved in war-time activities on behalf of the U.S. Government. As a sugar chemist he had been interested in active carbon for decolorising solutions and when in May 1917 the problem of protection against poison gas became urgent he was asked by Dr. Alsberg to undertake work on the large-scale production of active carbon. Although Hudson's part of this project was soon completed and he returned to the Bureau of Chemistry in October 1917 his experience had a strange and unexpected sequel. At the end of the war he decided to resign from the Bureau and try his luck as a consulting chemist in Trenton, New Jersey, in the fields of active carbons, yeasts, and malt syrups. This period lasted for 4 years (1919—1923) and came to an end when F. J. Bates, Chief of the Polarimetry Section of the National Bureau of Standards, offered him a research post in which he would be free to carry out fundamental studies in the field of sugar chemistry—an offer which he tells us he

accepted with delight. A period of five years devoted to brilliant and fruitful investigation then followed, broken only by a period of leave of absence spent in scientific work in Honolulu. He now was in a position to attract mature collaborators to his laboratory and in much of the work carried out at the National Bureau of Standards during the five years 1923—28 he was assisted by researchers who came to hold high positions in the world of science. Amongst them, for example, were to be found A. Kunz, C. B. Purves, E. Pacsu, W. C. Austin, M. L. Wolfrom, together with H. S. Isbell, Miss O. Hartley, and Miss E. Montgomery who were at that period regular employees of the Bureau.

Another important change came in 1929 when Hudson was offered the Professorship of Chemistry in the United States Public Health Service. He hesitated over acceptance since conditions at the Bureau offered him ample opportunity for the work he was most interested in, and he was less certain whether the Public Health Service would give him equal freedom. In the end he decided to make the change, swayed by the belief that the importance of the carbohydrate group in problems of nutrition would always call for fundamental research in that field. In this he was fully justified and the years from 1929 to 1951 which he spent at the National Institutes of Health were amongst the happiest and most fruitful of his career. He found that ample funds were provided for fundamental research and, writing many years later, he paid a warm tribute to the generous and friendly encouragement he received both in Washington and in Bethesda, Maryland, where the N.I.H. laboratories were situated from May 1941. "My experience," he states, and his remarks are of general import, "of about thirty years in research under three Departments of the Federal Government (Agriculture, Commerce and Federal Security Agency) has convinced me that those offices of the Government which are primarily concerned with matters of science can best render a high grade of public service if the spirit of fundamental research is encouraged among the personnel. Moreover I believe that in the choice of personnel for such government offices an innate and studious interest in fundamental research should be a major criterion of selection."

In the year after his appointment to the professorship Hudson travelled to Europe to attend the meetings of the International Union of Chemistry at Liége. The occasion was an important one for him since a conference on carbohydrate chemistry had been arranged and Hudson was taking the opportunity to present a complete system of ring structures for the simple sugars and their glycosides based on optical rotatory data interpreted in terms of the rules of isorotation. In many important instances, for example, methyl α-mannoside, the ring structures so deduced were at variance with those put forward by Haworth and Hirst on the basis of evidence obtained by the methylation procedure. So sure was Hudson of the accuracy of the principle of optical superposition that he claimed to have proved the inaccuracy of the methylation method. The outcome of the conference was in many ways a severe disappointment to Hudson. At an early stage of the meetings Haworth arranged a private discussion at which Hudson, C. B. Purves, Haworth, and the writer took part. The whole question was considered in detail and Hudson was told of the latest experiments of the Birmingham School from which it emerged that the rotational anomalies of the mannose group of sugars were not connected with ring structure, but involved departures from the isorotation rules which necessitated the abandonment of Hudson's scheme of structural proof. It is a measure of the real greatness of the two men that a situation which might have led to much friction was in fact the occasion for cementing a firm bond of friendship which was broken only by Sir Norman Haworth's death twenty years later.

The meetings at Liége had lasting effects in other respects also. In Hudson's later years he stressed the need for obtaining complete and often repeated proofs of structure, and his interest in theoretical matters was less pronounced. Another, and a highly important result of these controversies with Haworth, was the application to the sugar group of the periodate method of oxidation. In Hudson's own account of this development he writes "The new experimental results from methylation data which Haworth and Hirst presented at that Conference led me to return home with grave doubts of the validity of the views that I had advanced on the basis of my interpretation of rotatory relations. Therefore I sought to find some way by which evidence on this question could be obtained that would be independent of both methylation data and relations. The result is well known to organic chemists. By applying the periodate oxidation reaction of Malaprade to carbohydrates of many types, the workers in our laboratory were able to obtain the desired independent evidence. It confirmed the views of Haworth and Hirst in all respects. I look back on this conflict of views between Haworth and myself, which aroused much interest and discussion among organic chemists at the time, without a feeling of regret; the difference of opinion at least hastened the application of Malaprade's beautiful reaction to the study of carbohydrate structures and thereby gave to all a new tool of great usefulness, the value

of which is evident from its extensive and increasing use in present carbohydrate researches in many laboratories."

The years spent at the National Institutes of Health saw the publication of much of Hudson's best work. He attracted to his laboratory many workers who have subsequently come to occupy important positions of leadership in chemical research both in the U.S.A. and in other countries. As time went on there appeared to be no sign of slackening in interest or in his astonishing powers of concentrated work and to all who knew him it came as a great surprise that in 1951 he had reached the age of 70 and was due to retire. Nevertheless retirement to him meant little in the way of relaxation. It gave him more time to devote to editorial work for the series of volumes of "Advances in Carbohydrate Chemistry" in the inauguration of which he had played a large part. He continued to be interested also in drawing up rules of nomenclature for the carbohydrate group and played a prominent part in the discussions which resulted in the set of rules which in all essentials have now been jointly agreed upon by both American and British carbohydrate workers.

Another activity in which he maintained great interest was the "Starch Round Table" which he, Norman F. Kennedy, and William B. Newkirk started in 1939 as an annual conference at which chemists, mainly from the United States and Canada but with invited guests from other countries, could meet to discuss problems in the chemistry and technology of starch and related carbohydrates. The number of those attending is kept small and the discussions, which are usually held in some pleasant country resort, are informal and extraordinarily successful.

Hudson had little time to enjoy such leisure as his official retirement brought him. While still busily engaged in preparing for publication reports of work which had been completed before he left the National Institutes of Health, and in editing a new volume of the "Advances in Carbohydrate Chemistry" he died suddenly on December 27th, 1952, at the age of 71. By his death the world lost one of its leading exponents of organic chemistry whose long period of activity covered a decisive phase in the development of our knowledge of the carbohydrates. He was an inspiring leader and his influence is spread far beyond his own laboratory and is seen in many flourishing schools of research established by his pupils and associates. Friendly and informal in manner he nevertheless inspired in those he met a wholesome respect and admiration, and the essential bigness of his character could not be hidden by his outward informality. He demanded much of himself and expected it of those collaborating with him. Generally patient and sympathetic as a supervisor of research and in discussions there was nevertheless one thing which moved him to wrath—pretentiousness and glib argument based on what he considered to be insufficient experimental evidence. His own standards in this were extraordinarily high and one of his major contributions to knowledge lies in the innumerable exact descriptions he has given for the preparation of sugars and sugar derivatives of the highest degree of purity It may be said of him more truly than of most to whom the remark is applied that he lived for his work. He had a fund of stories of life in his beloved southern states and was most entertaining in conversation, but his heart lay really in carbohydrate chemistry and in matters closely related to it such as the growing of plants which contained rare sugars. Many tales are told of the intense concentration he invariably brought to bear on problems of the moment. In his laboratory everything, no matter how urgent, had to wait when Hudson was crystallising some intractable syrup. More awkward still was the predicament in which he and many others found themselves when Hudson, driving his motor car, went into an apparent trance while waiting for traffic lights to change, having just then had an inspiration concerning a possible proof of the structure of turanose.

Hudson was married four times. By his first wife he had a son and two daughters. The son, William Abbott, born in 1907, served as a corporal in the Eighth Air Force and died in England early in 1945 while on active service.

Despite the difficulties Hudson encountered in early life before he found a post in which his special qualities could reveal themselves, the novelty and importance of his work was quickly recognised. As early as 1912 Emil Fischer spoke of Hudson's Rule for lactones of the sugar group, and in 1916 he was awarded the Nichols Medal of the New York Section of the American Chemical Society. Election to membership in the National Academy of Sciences came in 1927. The Chicago Section of the American Chemical Society gave him the Willard Gibbs Medal in 1929, the Washington Section the Hillebrand Prize (1931), and the Northeastern Section the Richards Medal (1940). The American Chemical Society awarded him the Borden Medal in 1941 and he received the Cresson Medal of the Franklin Institute in 1942. He was a member also of the Kaiserlich Deutsche Akademie der Naturforscher (Halle). In May 1949 he was elected

to the Honorary Fellowship of the Chemical Society, and in the following year he received the first Federal Security Agency Award and the Grand Prize of the Sugar Research Foundation.

Hudson derived very special satisfaction from the award of the Honorary degree of Doctor of Science given him by Princeton University at their Bicentennial Convocation on 22nd February 1947. Another of his great joys was the possession of a gold watch and chain which had belonged to Emil Fischer. After his death these were returned to H. O. L. Fischer. The originals of all his medals he gave to Princeton.

In 1946 his friends in industry and in academic circles combined to honour his 65th birthday by holding a symposium and publishing in book form the 247 original papers which had come from Hudson's laboratories up to the end of June 1945. The occasion was marked by a banquet under the auspices of the Division of Sugar Chemistry and Technology of the American Chemical Society at which one of the appreciatory addresses was given by Sir Norman Haworth. Five years later, on January 25th, 1951, another banquet was held in his honour to celebrate his 70th birthday. This was attended by members of the various divisions of the National Institutes of Health, and by representatives from many other government departments, Universities, and Research Institutes. Congratulatory messages were received from friends and admirers on both sides of the Atlantic and many speakers paid tribute to the contributions made by Hudson to the cause of science during the previous half-century. It was, however, particularly appropriate that one of the speakers should be Nelson K. Richtmyer who had been a colleague of Hudson's at Bethesda since 1934, and spoke as a representative of the "Undergraduates of Hudson University." For great as Hudson's own contributions had been both in theory and in experimental work, he has an even greater claim to fame in the inspiration which he gave to so many who came under his influence and are now actively engaged in carbohydrate chemistry in centres to be found all over the world.

Hudson's first researches were concerned with problems of mutarotation and much of his later work can be regarded as a logical development of his early discoveries. When he began work extensive information was available about the physical properties of the monosaccharides and thanks mainly to the insight of Emil Fischer the configurations of many of them were known. But the detailed structures were in every case obscure and little was known with certainty concerning the phenomenon of mutarotation. Many suggestions had been made, including a change from an anhydrous to a hydrated form by analogy with the hydration of lactones. Alternatively a change from a supermolecular aggregation to a unimolecular form, or from open-chain aldehydic to cyclic hemiacetal forms of the type then accepted for the two methyl glucosides, had been postulated. The case of lactose which Hudson chose to study was particularly complicated for no less than two anhydrous and two hydrated forms were known. In the first instance he regarded the problem as one of the physical chemistry of hydration and by quantitative measurements of the heats of solution and other observations he showed that one of the supposed forms of lactose was not a chemical individual but a mechanical mixture of two of the other forms. In 1903 he demonstrated that this mutarotation involved a reversible unimolecular reaction in which two of the forms came into equilibrium. Proof of this came from kinetic studies which involved for the first time the use of the powerful technique by which the rate of solution of a single pure form of the sugar was studied. For example, the concentration of α-lactose hydrate was maintained constant by continuous shaking of the solution at 0° in the presence of an excess of the powdered solid, whilst the increase of solubility with time and the accompanying rotation changes were studied. By an extension of this device it subsequently became possible, given one form of a sugar in a pure condition and a knowledge of the mutarotation data, to calculate the rotation of the anomer. In this early work on lactose it became clear that hydration of the α-form was a very rapid reaction independent of the mutarotation reaction, which could be regarded as α-lactose $\rightleftarrows$ β-lactose. In 1908 he summarised the results obtained with lactose by the accompanying equation in which the second balanced reaction is the one involving

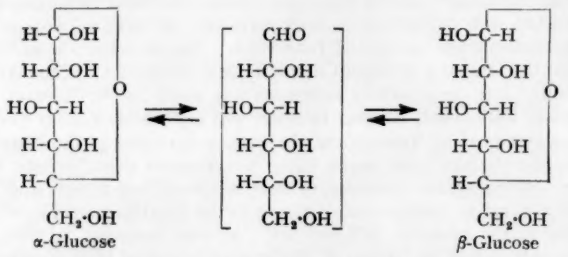
Mutarotation of lactose

$$\alpha\text{-Form} + H_2O \underset{\text{(Fast)}}{\rightleftharpoons} \text{hydrated form} \rightleftarrows H_2O + \beta\text{-form}$$

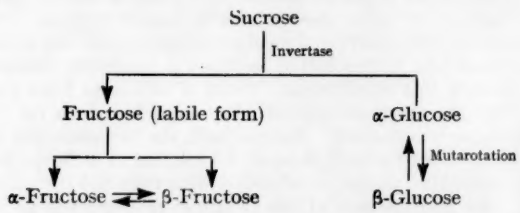
mutarotation. The way was prepared therefore for the modern concept that mutarotation involves the interconversion of cyclic forms of a reducing sugar. This had in fact been suggested by von Lippmann in 1895, but no detailed mechanism could then be put forward. That mutarotation involved a reversible reaction was in fact first suggested by T. M. Lowry (1899), but Hudson's independent work provided the first experimental proof. Arising out of these studies came his investigation into the effects of hydrogen and hydroxyl ions on the rate of mutarotation

of glucose, during which he established the relations generally accepted, and incidentally provided yet another method for determining the dissociation constant of water. The formula for the rate of mutarotation of glucose at 25° in aqueous solution was expressed as $k = 0{\cdot}0096 + 0{\cdot}258[H^{\cdot}] + 9750[OH']$.

It was perhaps fortunate that the mutarotation phenomena shown by lactose were essentially straightforward in character despite the complications introduced by the existence of crystalline



hydrates, and involved only the reversible transformation of two forms possessing the same ring structure. In other instances which have been studied more recently much greater complexities arise owing to the interplay of the α- and the β-varieties of both furanose and pyranose ring structure, with the additional possibility of the presence also of the open-chain aldehydic or ketonic form. Hudson's early work paved the way for investigations in these more difficult regions and he applied the new ideas himself in an examination of the changes which occur during the inversion of cane sugar by the yeast-enzyme invertase. As far back as 1890 O'Sullivan and Thomson had claimed that the inversion of sucrose by invertase was a unimolecular reaction, but the position had become confused as the result of later work which could not be satisfactorily interpreted until the nature of mutarotation had been ascertained. Hudson's work on lactose led him naturally to this more complicated problem. In a long series of articles he confirmed and extended the original work of O'Sullivan and Thomson, developing the physicochemical theory of rates of reaction to cover the new complications. One of the key experiments of this series involved the rapid hydrolysis of a quantity of cane sugar by use of a large excess of enzyme, when it appeared that the optical changes could be accounted for almost entirely by the mutarotation of the liberated reducing sugars. Shortly before this (1903), E. F. Armstrong had

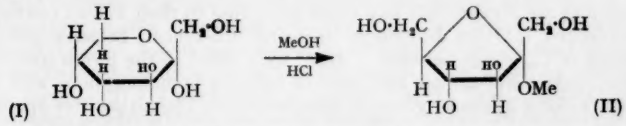


described his classical experiments on the correlation by enzymic methods of α- and β-glucose with the corresponding methyl α- and β-glucosides. This idea was then applied by Hudson in interpreting the detailed kinetic measurements made during the experiments on the hydrolysis of sucrose with invertase. It followed that the glucose residue in cane sugar was present as the α-glucoside. The fructose portion could not be identified and indeed the extremely labile β-fructofuranose which is now known to be the form in which the fructose first makes its appearance has never yet been isolated.

The results of this work were far-reaching, going much beyond the structural chemistry of sucrose. In the first place Hudson's pioneering researches did a great deal to establish a sound conception of enzyme action. He was the first to demonstrate the possibility of preparing invertase from yeast by rapid autolysis in the presence of water saturated with toluene. Salkowski had previously used toluene to prevent the putrefaction of the yeast during the autolysis, but Hudson employed it not merely as a bacteriostatic agent but as a chemical which induces a rapid autolytic reaction when there is sufficient of it present to saturate the mixture of yeast and water. His work in this field led also to the use of invertase in the exact analytical

determination of sucrose by the Clerget procedure, and by suitable modifications of the enzymic method it is possible to determine sucrose and raffinose in admixture. More important still, it must be remembered that general ideas on the mode of action of enzymes were uncertain, to say the least, at the beginning of the century and Hudson's work did much to discredit finally the view that the chemical activity of enzymes was governed by some unknown and obscure force. Writing in 1908 he said: "May it not be that other enzymic reactions are, after all, quite similar to the usual types of chemical catalysis and do not constitute a group that has unique laws of catalytic action as is now generally believed." So different is the present day outlook that it seems hardly credible that such words were considered necessary less than 50 years ago.

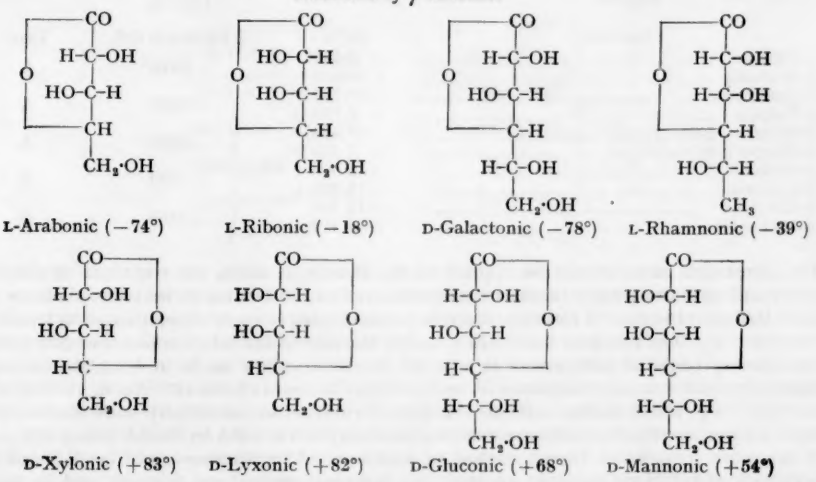
Hudson and his collaborators continued their interest in enzyme studies, particularly with regard to the fractionation and purification of the enzymic systems present in yeasts, and the mode of action of the purified enzymes on various substrates, Mildred Adams and N. K. Richtmyer being closely associated with much of this work. Similar problems relating to the action of the starch-splitting amylases were also investigated. One of the most spectacular results of the work on invertase came when Hudson and C. B. Purves showed that by the use of invertase it was possible to separate from the so-called "γ"-methyl fructoside, obtained by the controlled reaction of cold methanolic hydrogen chloride with fructose (I), a pure crystalline methyl fructoside having $[\alpha]_D$ +93° in aqueous solution. This was a typical "γ"-glucoside and was subsequently shown to be methyl α-D-fructofuranoside (II).



(I) (II)

One very important feature of this discovery was that it provided an accurate rotation of a member of the fructofuranoside group for use in connection with the isorotation rules which occupied Hudson's attention so markedly throughout his career. This aspect of his work once again followed directly and naturally from his early investigations on the mutarotation of lactose. In 1908 he began to collect from the chemical literature all the known specific rotations of the sugars and their derivatives. For the most part these numerical values constitute a chaos in which no signs of order have been detected, the exceptions to this statement being comprised

Rotations of γ-lactones.



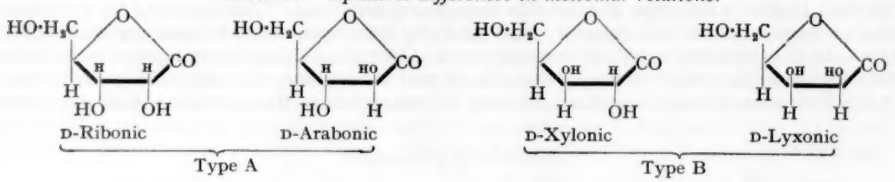
L-Arabonic (−74°) L-Ribonic (−18°) D-Galactonic (−78°) L-Rhamnonic (−39°)

D-Xylonic (+83°) D-Lyxonic (+82°) D-Gluconic (+68°) D-Mannonic (+54°)

in Hudson's Rules of Isorotation. The regularities he discovered are indeed most remarkable and when used with due caution they provide sugar chemists with a valuable means of elucidating structure, but perhaps the most astonishing thing about them is that they should be valid at all, since there is no sure ground in physical theory for the underlying principle of optical super-

position first enunciated by van't Hoff. Some idea of the problems involved may be gained from a consideration of the first of these rules which dealt with the sign of rotation of the lactones of the sugar acids. The rule was enunciated in 1909 (published early in 1910) in the following words: "Lactones of dextrorotation have the lactonic ring on one side of the structure, lactones of levorotation have it on the other, and the position of the ring shows the former position of the OH group on the γ-carbon atom." The rule was shown to apply to 24 different lactones which were then known and since 1910 many others have been added to the list. Some typical examples are given in the accompanying Table. This rule has been widely used by sugar chemists and in the great majority of instances it has been a reliable guide to structure, giving results which are in agreement with those ascertained by other methods. Much has been written of the high probability of the accuracy of this rule—stated to be millions to one in its favour—yet in the form in which it was first enunciated it fails in the case of D-allonic γ-lactone ($[\alpha]_D$ $-6{\cdot}8°$). This case however falls into line if the stipulation is made that when the OH is on the right in the Fischer projection formula the lactone is more dextrorotatory than the corresponding free acid. This rule is a qualitative expression and for many years Hudson believed that principles of optical superposition could not hold in the lactone group. This principle, first enunciated by van't Hoff, requires that if the partial rotation due to any one of several asymmetric carbon atoms is represented by $+A°$ then on replacement of that group by its mirror image the latter should be responsible for $-A°$ of the rotation of the new compound. In 1939 however he came to the conclusion that the isorotation and the superposition rule did apply approximately provided the lactones are divided into two types according to their known configurations. For instance, the molecular rotation differences (epimeric differences) between pairs of γ-lactones epimeric in respect of $C_{(2)}$ range between $-3400°$ to $-4000°$ in the group containing the pairs ribonic–arabonic; galactonic–talonic and pairs of lactones homomorphous with these, whereas in the other series (xylonic–lyxonic; gluconic–mannonic; etc.) small positive epimeric differences are found.

Lactones. Epimeric differences in molecular rotations.



Lactone	$[M]_D$	½ Epimeric diff.	Type
D-Ribonic	+ 2,660°		
D-Arabonic	+10,600	−3970°	A
D-Galactonic	−13,780		
D-Talonic	− 6,170	−3800	A
D-Manno-D-galaheptonic	−15,400		
D-Manno-D-taloheptonic	− 7,430	−3980	A
D-Xylonic	+13,590		
D-Lyxonic	+12,200	+ 690	B
D-Gluconic	+12,100		
D-Mannonic	+ 9,170	+1460	B

The isorotation rules cannot be applied to the free sugar acids, the rotations of which are usually small, and the greater regularities encountered in the lactone series probably have their origin in the great increase in rotation which is found in most cases to accompany ring formation. The centre at $C_{(4)}$ then becomes dominant in fixing the sign of the rotation but the complexity of the underlying physical phenomena is seen in the observation made in later studies of the anomalous optical rotatory dispersion of certain sugar lactones (Hirst and Wood, 1936) that the term $k/(\lambda^2 - \lambda^2_0)$ which really controls the sign of rotation in conformity with Hudson's rule contains a wave-length constant corresponding to absorption of light by the CO group at $C_{(1)}$. It is all the more remarkable therefore that so many useful regularities could be deduced from observations of rotations made at an arbitrary temperature and wave-length and in the one solvent (water).

If the lactone ring is not present, then for many derivatives of the acid the centre at $C_{(2)}$ becomes dominant and several extremely useful rotation rules were developed by Hudson in this field. For example, the rotations of the phenylhydrazides of the acids conform to the rule (put

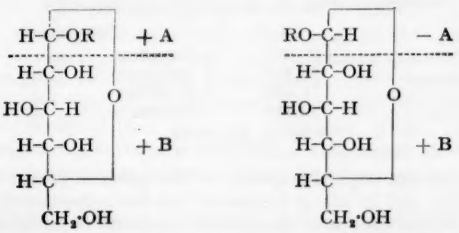
forward in 1917) that the direction of rotation is to the right if the hydroxyl on the α-carbon atom is on the right in the Fischer projection formula, and its opposite.

Rotations of phenylhydrazides and amides of aldonic acids ($[\alpha]_D$ in water).

Acid	Rotation of phenylhydrazide	Rotation of amide	Configuration of $C_{(2)}$
D-Gluconic	+12°	+33·8°	Right
D-Gulonic	+13·7	+16·1	,,
D-Galactonic	+11	+36·7	,,
D-α-Glucoheptonic	+ 9·3	+10·6	,,
D-α-Mannoheptonic	+21	+28	,,
D-α-Galaheptonic	+ 8·5	+14·3	,,
D-Mannonic	− 8	−29·9	Left
D-Arabonic	−14·5	−38	,,

An exactly similar rule was found to apply in the amide group (1918) and also to the benziminazole derivatives of the aldonic acids (Richtmyer and Hudson, 1942). All of these have had a wide use in the development of sugar chemistry, their value being particularly evident in the determination of the configurations of the epimeric acids formed during the cyanohydrin synthesis of higher sugars.

Equally important results followed from Hudson's efforts to bring some order into the rotational relations exhibited by the sugars, their glycosides, and other derivatives. Starting with observations (1909) of the approximate constancy of the differences between the rotations of the known methyl α- and β-glycosides Hudson proceeded to build a vast edifice of structural relations on numerical data with the aid of two isorotation rules, which he reformulated in 1930 in the following terms. (1) " The rotation of carbon 1 in the case of many substances of the sugar group is affected in only a minor degree by changes in the structure of the remainder of the molecule." (2) " Changes in the structure of carbon 1 in the case of many substances of the sugar group affect in only a minor degree the rotation of the remainder of the molecule." It is worth mentioning that these rules go far beyond predictions which could be made from the van't Hoff theory of optical superposition. The latter assumed that the rotations contributed by a given set of asymmetric centres were additive, but in the various glycosides the centres in the bulk of the molecule are not identical and make various and very different contributions. According to the rules enunciated by Hudson the rotation of an alkyl glycoside is to be regarded as made up of two parts (1) A, contributed by $C_{(1)}$ and (2) B the sum total of the rotatory contributions of the other centres.



If these rules are valid it follows that the sum of the molecular rotation values, 2B, should have a numerical value characteristic of the sugar concerned and independent of the nature of R. On the other hand the difference of the rotation values, 2A, should be independent of the nature of the sugar, but will carry its own particular value. The value of B would be expected to vary for any one sugar according to the nature of the ring system present. For instance, the 2B value for the glucopyranose residue, calculated from the rotations of the ethyl glucosides is 24,000, whereas for the glucofuranose ring it is 2500. Now for glucose itself, when the rotation values for α- and β-glucose are used, 2B is 23,600, strong evidence being thus provided for the presence of the pyranose ring structure in α- and β-glucose.

The regularities hold over a very wide range including simple sugars, oligosaccharides, and polysaccharides and some typical examples will be found in the accompanying Tables, but no attempt can be made here to illustrate the wealth of material assembled by Hudson and his colleagues during some 40 years of work on these problems. At this point it is appropriate to make special reference to the lengthy series of investigations, with which the name of R. M. Hann

is particularly associated, on syntheses of the higher-carbon sugars and their derivatives, undertaken primarily in order to obtain data for comparison of the rotations of these substances with those of the configurationally similar hexoses and pentoses. All types of derivatives were prepared and examined and the mass of information thus obtained concerning methods of preparation of sugars and their derivatives, together with the accurate determinations of the physical properties of the pure substances, must be regarded as one of Hudson's major achievements in organic chemistry.

By means of sets of coefficients derived by aid of the rules from the rotations of known substances the rotations of substances then unknown were calculated, and on synthesis of these materials excellent agreement was usually found between the observed and the predicted values. So certain did the validity of the rules appear to be that to those working in the field the failure

Substance	$[\alpha]_D$	Molecular rotation	2A	Substance	$[\alpha]_D$	Molecular rotation	2A
α-D-Glucose ...	+109°	19,600	16,000	α-D-Lyxose	+ 5·5	825	6,225
β-D-Glucose ...	+ 20	3,600		β-D-Lyxose	−36	−5400	
α-D-Galactose	+140	25,200	15,700	α-L-Rhamnose ...	− 8	−1300	10,050
β-D-Galactose	+ 53	9,500		β-L-Rhamnose ...	+54	8750	
α-D-Lactose ...	+ 86	29,400	17,400	4-β-Glucosido-α-mannose	+20	6840	7,182
β-D-Lactose ...	+ 35	12,000					
α-D-Mannose ...	+ 30	5,400	8,460	4-Glucosido-β-mannose	− 1	− 342	
β-D-Mannose ...	− 17	−3,060					

Illustrations of the first and second rules of isorotation.

Substance	$[M]_D$ (in water)	2B	2A
Methyl α-D-glucoside	+30,830°		37,460
Methyl β-D-glucoside	− 6,630		
Methyl α-D-xyloside	+25,200		35,900
Methyl β-D-xyloside	−10,700		
Methyl α-gentiobioside	+23,318		36,118
Methyl β-gentiobioside	−12,800		
Methyl α-D-glucoside	+30,830	24,200	
Methyl β-D-glucoside	− 6,630		
α-D-Glucose	+20,300	23,720	
β-D-Glucose	+ 3,420		
Glycol α-D-glucoside	+30,350	23,510	
Glycol β-D-glucoside	− 6,840		

Values of 2A *for methyl glycopyranosides.*

Substance	2A	Substance	2A
D-Glucose	37,500°	D-Galactose	38,220°
D-Glucose *	39,300	L-Arabinose	37,460
D-Glucofuranose *	38,300	D-Mannose	28,930
D-Gulose	39,390	L-Rhamnose	28,140

* Ethyl glucoside.

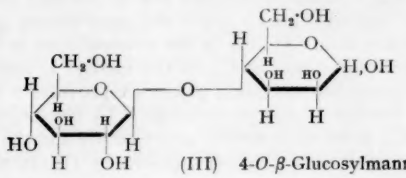
of a new substance to conform implied impurity of the material under examination rather than an exception to the rules, and in many instances this has subsequently been found to be the correct explanation. Certain groups of substances, however, required special treatment. It is perhaps not unexpected that the rotational relations between the various substituted phenyl glucosides proved to be complicated, and, as in the case of the lactones, attempts to go to extremes by calculating coefficients for each of the carbon atoms of the hexose chain achieved little. Nevertheless the area of agreement was large and that of anomalous cases small, with the result that Hudson could write in his summarising paper of 1930:

"The correlation of structures and optical rotating powers among substances of the sugar group . . . has yielded so far the following seven principal results: (1) proof that the stable lactones of the monobasic acids derived from the monosaccharides are γ-lactones, (2) a system of nomenclature for distinguishing the alpha and beta forms of the sugars and their principal derivatives, (3) determination of the hitherto unknown configurations of some of the sugars (*e.g.*, rhamnose, fucose, gluco-octose), (4) proof that amygdaloside is a glycoside of gentiobiose, (5) proof that several of the ketonic sugars (sorbose, tagatose, mannoketoheptose and glucoheptulose) exist in solution only as alpha forms and consequently do not exhibit mutarotation, (6) proof that the methylation of glycosides often involves a ring shifting, and (7) proof of the ring structure

of most of the monosaccharides and compound sugars." The first five of these claims have been upheld, but (6) and (7) which had no foundation in fact require some further discussion.

Reference to the Tables of 2A values reveals that for glucose, galactose, and certain other sugars in which the OH groups on $C_{(2)}$ and $C_{(3)}$ are situated *trans* to one another, the value of 2A is approximately 38,000. On the other hand, for mannose and rhamnose and similar sugars in which these OH groups are *cis* to one another the value of 2A is only some 29,000. Hudson interpreted this as indicating a difference in ring form between the methyl α-mannoside and the methyl β-mannoside, rather than a failure of the rules. A furanose structure was arbitrarily assigned to methyl α-mannoside and on this basis a complete scheme of sugar structures was erected, consistent as regards rotation values, but opposed to the chemical evidence based on the methylation procedure which clearly demanded a pyranose structure for methyl α-mannoside. The clash was direct and admitted of no compromise. Hudson maintained his belief in the isorotation rules and was inevitably compelled to claim that methylation of methyl α-mannoside involved a change of ring from the furanose to the pyranose structure. At this stage fate played a trick on him which he scarcely deserved. The rotations of the alkyl glucofuranosides became known and by sheer coincidence the molecular-rotation difference between corresponding members of pyranose and furanose type was close to 10,000, this value being identical with the amount by which the rotation of ordinary methyl α-mannoside differed from Hudson's calculated value for the pyranose form of methyl α-mannoside. He hailed the new evidence as convincing proof of the correctness of his views and fitted it into the comprehensive scheme of structures for monosaccharides and disaccharides and their derivatives which is elaborated in the paper presented at the International Conference at Liége (1930).

It was inconceivable to organic chemists who were familiar with the Purdie reaction that such a change of ring could take place during methylation, and the Birmingham School sought a final decision by preparing from cellobiose a substance (III) (4-*O*-β-glucosylmannose) in which the occurrence of a furanose ring in the mannose residue is ruled out by the nature of the disaccharide linkage. It was found that the rotations of the α- and the β-form of this disaccharide give a value of 2A (7182) similar to that found for α- and β-mannose but very different from the larger



(III) 4-*O*-β-Glucosylmannose.

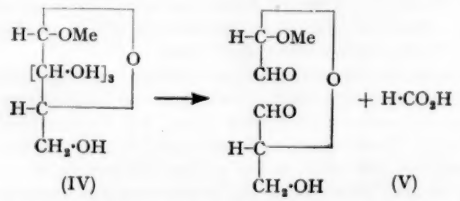
value (16,000) given by glucose, galactose, and other sugars of this group, all of which have *trans*-situated hydroxyl groups at $C_{(2)}$ and $C_{(3)}$. Similar results (2A = 7500) were found when the corresponding disaccharide 4-*O*-β-galactopyranosylmannose was synthesised from lactose. It was then clear that a great part of the structural use of Hudson's isorotation rules must be abandoned and it is now accepted that mannose, rhamnose, lyxose, and other sugars which possess *cis*-hydroxyl groups at $C_{(2)}$ and $C_{(3)}$ must be treated separately, their rotational behaviour being influenced by their configuration, possibly by way of variations in the conformation of the pyranose ring.

Hudson accepted, albeit with some reluctance, the evidence based on the 2A rotational values for 4-glucosyl- and 4-galactosyl-mannose, but returned to the United States determined to find a completely independent method, resting neither on isorotation rules nor on methylation processes, by which the ring structure of glycosides could be determined. In the first instance he examined exhaustively the possibility that methyl α-mannoside might be resolvable into two compounds, as he had previously demonstrated with a double crystal of methyl α- and β-xylosides. This, however, proved to be a fruitless task and it was not until some time later that observations by E. L. Jackson on the oxidation of methyl glucoside by alkaline hypobromite brought into discussion Malaprade's work (1934) on the oxidative fission of glycols, and led Hudson to realise that the very method he had been looking for was available in oxidation by periodic acid. The reaction is highly selective and in Hudson's hands it was applied with conspicuous success from 1936 onwards to a wide range of problems in carbohydrate chemistry. The main reactions are shown in the accompanying equations and it will be seen that differentiation can readily be made between furanose and pyranose rings in methyl glycosides. For example, the α-form of methyl D-hexopyranoside (IV) gives rise to a dialdehyde

(V) containing 5 carbon atoms and one mol. of formic acid, two mols. of periodic acid being required. No formaldehyde is produced. On the other hand, the corresponding methyl α-D-furanoside would yield one mol. of formaldehyde but no formic acid, and would again con-

$$R'\cdot CH(OH)\cdot CH(OH)\cdot R' \longrightarrow R\cdot CHO + R'\cdot CHO$$
$$R'\cdot CH(OH)\cdot CH(OH)\cdot CH(OH)\cdot R' \longrightarrow R\cdot CHO + H\cdot CO_2H + R'\cdot CHO$$
$$HO\cdot CH_2\cdot CH(OH)\cdot R \longrightarrow H\cdot CHO + R\cdot CHO$$
$$CH_3\cdot CH(OH)\cdot CH(OH)\cdot R \longrightarrow CH_3\cdot CHO + R\cdot CHO$$

sume two mols. of periodic acid during the oxidation. The consumption of periodic acid and the nature of the reaction products provide evidence of the nature of the ring system. The reaction, however, goes much further and gives important information when applied to many other problems. For instance, Hudson and Jackson used it to prove the configuration at $C_{(1)}$ of the methyl α- and β-glycosides. Inspection of the formula shown above reveals that during the oxidation of a methyl α-D-hexopyranoside the optically active centres at $C_{(2)}$, $C_{(3)}$, and $C_{(4)}$ disappear. Now the configuration at $C_{(5)}$ determines the series, D- or L-, to which the sugar belongs, whilst the configuration at $C_{(1)}$ controls the type of glycoside. It follows that in the D-series of sugars all those methyl hexopyranosides which have the methoxyl group below the



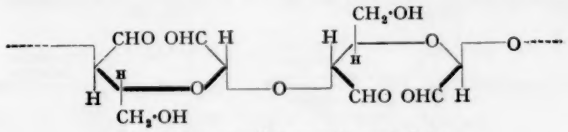
plane of the ring in the Haworth formula should give rise to one and the same dialdehyde (*A*). Similarly all those having the methoxyl group above the plane should give rise to one and the same dialdehyde (*B*) which differs from (*A*) only in the configuration at the carbon atom which was formerly $C_{(1)}$. Since the configuration at $C_{(1)}$ of the methyl α- and β-glucosides is known from other considerations the periodate oxidation procedure provides a method for determining the configuration of all the methyl D-glycopyranosides. In the pentapyranoside series the position is even simpler since $C_{(5)}$ is not an optically active centre and the two substances obtainable as reaction products (*A* and *B* with $CH_2\cdot OH$ replaced by H) are now mirror images. In

practice the aldehydes are somewhat awkward to handle and Hudson and Jackson introduced a further stage of oxidation in which the ·CHO groups were transformed into $\cdot CO_2H$, the final products being isolated as salts. In the hexose series it was found that the α-D-glycosides gave rise to an easily crystallisable strontium salt, whereas the barium salt was preferable for the β-glycosides.

Evidence for the configuration at $C_{(1)}$ can be obtained even more simply by another method worked out in Hudson's laboratory. The various glycosides have different rotations but as oxidation proceeds some of the carbon atoms lose their dissymmetry and in the case of any methyl glycoside of the D-hexopyranose group the final product must be either (*A*) or (*B*). Since (*A*) and (*B*) differ markedly in their rotatory powers, observations of the rotation of the solution during the oxidation will provide evidence for assigning any given methyl hexopyranoside or methyl pentofuranoside to the α- or the β-group. Closely similar methods permit corresponding results to be achieved for the pentopyranosides.

The importance of this new approach lay in the first place in the independent proofs thus provided of the structure of the methyl glycosides and of their configuration at $C_{(1)}$. In all the instances examined the results were in complete agreement with those of the methylation method in regard to the size of ring, and the configurations of the methyl glycosides thus determined were identical with those previously allocated on the basis of the isorotation rules.

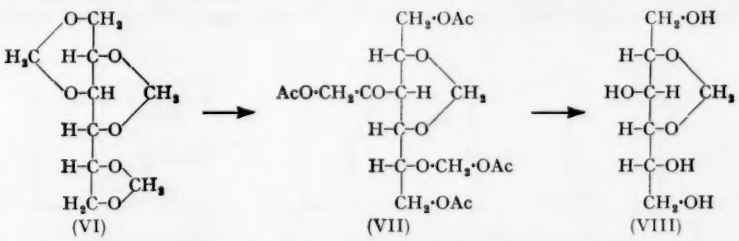
Numerous applications of this method of oxidation were soon made to sugar anhydrides, to partly substituted sugars, and to cyclic acetals, and during these developments Hudson made some of his rare incursions into the polysaccharide field. Here again he, like many who have followed him, found periodic acid to be a most versatile reagent. Applying it to cellulose and starch in 1938 Jackson and Hudson obtained evidence in support of the accepted ring structures of the glucose residues present in these polysaccharides, each 1 : 4-linked glucopyranose unit giving rise to a dialdehydic structure on consumption of one mol. of periodic acid per residue.



Oxidation of cellulose with periodate

The products, which are polymers built up of residues of erythrose and glyoxal, still have a high molecular weight, but they are extremely sensitive to alkali and Hudson did not pursue the investigations.

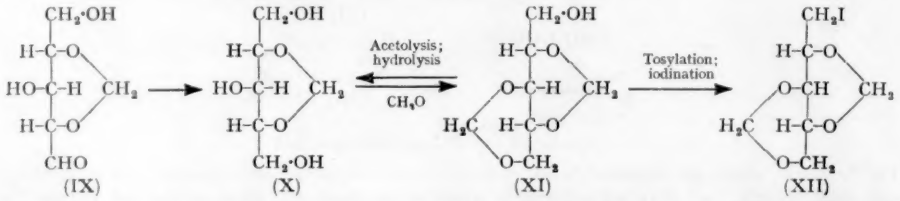
The periodate oxidation method provided a new tool for the investigations of the chemistry of the cyclic acetals of the sugar alcohols, and much of Hudson's later work was concentrated in this field which has yielded results of great theoretical interest in addition to new and useful methods of synthesis. With its development the name of R. M. Hann is closely associated. The general scope of the problems may be illustrated by reference to the cyclic methylene acetals of D-sorbitol. When formaldehyde combines with D-sorbitol a trimethylene derivative is formed and evidence is required concerning the structure of this substance. It cannot be assumed that the six hydroxyl groups act in consecutive pairs giving three five-membered rings, leading to the structure 1 : 2-3 : 4-5 : 6-tri-*O*-methylene D-sorbitol, since it is known that 5-, 6-, and 7-membered rings can be formed in similar reactions and that the course of the reaction is much influenced by the stereochemical configuration of the hexitol. It was proved, indeed, that this particular tri-*O*-methylenesorbitol (VI) contains rings in which the methylene groups engage the hydroxyl groups at positions 1 : 3, 2 : 4, and 5 : 6, severally, two of the rings being six-membered and the other five-membered. Proof of structure was derived from the following considerations. When the trimethylene derivative was treated with acetic anhydride and acetic acid containing a little sulphuric acid two of the rings are cleaved and in earlier work it had been shown that this reagent will break only those O–C bonds in which a primary alcoholic group is involved, with formation of a tetra-acetyl derivative (VII). Methylene residues attached through secondary alcoholic



(VI) (VII) (VIII)

positions are unaffected. Deacetylation now yielded a monomethylene derivative (VIII) in which the points of attachment of the ring were shown in the following way to be $C_{(2)}$ and $C_{(4)}$. The substance reacted with one mol. of periodic acid with formation of one mol. of formaldehyde and one mol. of a monomethylenepentose sugar (IX). It followed that the monomethylenesorbitol contained only one unsubstituted glycol unit and that this glycol unit included a primary alcoholic group. Reduction of (IX) gave a methylenepentitol (X) which was stable to periodic acid and was shown to be derived from xylitol. It followed that the methylene group in the pentitol and hence also in the monomethylenesorbitol was attached in the 2 : 4-position. If now the possible methylene acetal structures are limited to those containing 5-, 6-, or 7-members it follows that the original trimethylenesorbitol had the structure (VI). Confirmatory evidence was found in the discovery that in the reaction between D-sorbitol and formaldehyde a dimethylene derivative is also produced and this was shown independently to have the structure 1 : 3-2 : 4-di-*O*-methylene-D-sorbitol. The monomethylenexylitol (X) is internally compensated and

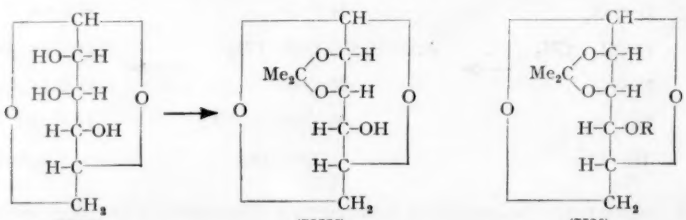
optically inactive, but when condensed with formaldehyde it gives a racemic dimethylene derivative (XI) in which the single OH group is primary alcoholic in nature, as shown by the results of the reaction with toluene-*p*-sulphonyl chloride, followed by treatment of the product with sodium iodide in acetone (to give XII). Selective acetolysis of the dimethylenexylitol followed by hydrolysis of the acetyl and acetoxymethyl groups gives back the *meso*-2 : 4-*O*-methylenexylitol (X). The structures of all these compounds in the sorbitol and xylitol series were thus established by unambiguous inter-related methods.



(IX) (X) (XI) (XII)

This however is merely a simple example selected to illustrate the types of methods employed by Hudson, Hann, and their collaborators in wending their way through all the intricacies of the 5-, 6-, and 7-membered acetal rings which were encountered in their detailed studies of the acetals of mannitol, sorbitol, dulcitol, adonitol, arabitol, xylitol, fucitol, iditol, rhamnitol, *epi*rhamnitol, *gluco-gulo*-heptitol, talitol, and perseitol. In this work much has been learned of the unexpected effects of *cis–trans*-isomerism, of the migration of ester groups, and of the relative reaction rates for the formation of the various types of ring systems. It appears, for instance, that the most favourable positions for methylene acetal formation involve β-situated secondary hydroxyl groups *cis* to one another in the Fischer projection formula, giving rise to a six-membered ring. The next most likely reaction would involve a 7-membered ring formed about secondary hydroxyl groups which are *trans* and γ in their relations. Next comes a 6-membered ring involving a primary alcoholic group. Formation of a five-membered ring including a primary alcoholic group is still less probable in competition with the other possibilities.

Much progress has been made also by Hudson and Hann in the use of cyclic acetals for syntheses. An important starting point in this work was the D-mannosan (XIII) which can be obtained by the dry distillation of ivory-nut mannan. It readily yielded the 2 : 3-*O*-*iso*propylidene derivative (XIV) which possesses a free hydroxyl group at $C_{(4)}$. Methylation then gave the 4-*O*-methyl derivative (XV) and, after hydrolysis and opening of the anhydro-ring, 4-*O*-methylmannose was obtained, a substance of great interest in connection with the isorotation rules. Of still greater interest is the use of (XIV) as an intermediate substance in unambiguous routes to the synthesis of disaccharides. Condensation with acetobromo-D-glucose and acetobromo-D-

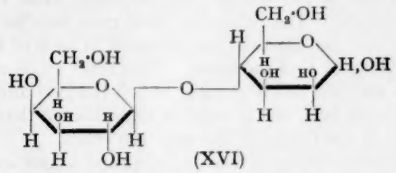


(XIII) (XIV) (XV)

galactose gave (XV) in which R was tetra-*O*-acetyl-β-D-glucosyl and tetra-*O*-acetyl-β-D-galactosyl respectively. The *iso*propylidene group was removed with acetic acid and the 1 : 6-anhydro-ring was opened by controlled acetolysis, the products being respectively an acetylated 4-*O*-β-glucosidylmannose and an acetylated 4-*O*-β-galactosylmannose from which the free sugars (III) and (XVI) were obtained. By a series of known reaction steps the epimers cellobiose and lactose were then prepared. These transformations provided for the first time by synthetic methods unambiguous confirmatory evidence of the structures previously proved by degradative procedures.

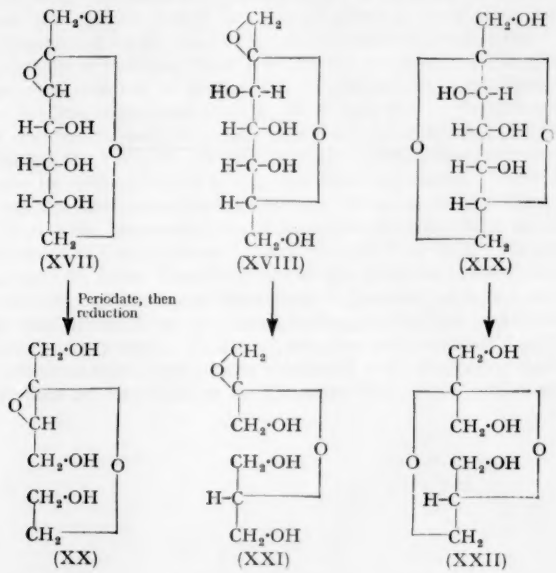
It is clear, therefore, that Hudson's work in the sugar field covered a wide range of topics and that in all he entered upon he made notable contributions. It is difficult to say which of these had the greatest influence on the development of carbohydrate chemistry, but there can be no

doubt of the inspiration given to other workers and of the lasting benefit to his subject provided by one of the less spectacular of his activities. He took a keen interest in the chemistry of naturally occurring substances, and he had a flair for devising methods of extraction and purification and for preparing in the purest possible state a host of derivatives, which he described in meticulous detail. When comments were made about this towards the end of his life he replied that all his early training had been in the exact measurements of physical chemistry and that his knowledge of organic chemistry was entirely self-taught. It is perhaps appropriate therefore to conclude this brief account by reference to a topic of this kind which spanned almost all his



(XVI)

working career. In 1917 La Forge and Hudson isolated from the plant *Sedum spectabile* a new sugar which was subsequently named sedoheptulose. At that time it was merely a chemical curiosity but it has recently assumed a quite unexpected importance by reason of its occurrence at an early stage in photosynthesis (Calvin). The chemistry of sedoheptulose is unusual and its study has been actively pursued by N. K. Richtmyer in Hudson's laboratories at Bethesda. The sugar has a configuration of the altrose type and gives rise to normal derivatives of pyranose structure. It resembles altrose but differs from most sugars in its capacity to give with acids an anhydro-derivative (sedoheptulosan), the structure of which has proved unexpectedly difficult to determine. Reaction with periodate revealed the presence of 3 contiguous secondary hydroxyl groups, indicating one of the three structures (XVII—XIX). The oxidation product after reduction and hydrolysis gave glycerol which could arise from (XXI) or (XXII) but not from (XX), and from this it followed that sedoheptulosan could not be (XVII) (1951; details published



(XVII) (XVIII) (XIX)

(XX) (XXI) (XXII)

posthumously in 1952). This conclusion was supported by the results obtained by methylation of the sedoheptulosan, followed by oxidative degradation. The product, contrary to earlier reports, was conclusively proved to be D-*arabo*trimethoxyglutaric acid. The final choice between (XVIII) and (XIX) rests on various pieces of evidence one of which involved a study of the rate of oxidation with periodate. A substance of structure (XVIII) would react only slowly

with the reagent after formation of the initial dialdehyde, whereas (XIX), the dialdehyde from which can act as a furanose sugar, would complete its uptake of periodate rapidly. The product would then be a formyl ester which would hydrolyse slowly, giving formic acid. This is precisely how sedoheptulosan reacts and the choice of (XIX) for its structure is confirmed by the failure of tetra-*O*-toluene-*p*-sulphonylsedoheptulosan to react at 100° with sodium iodide. Although this derivative contains a primary toluene-*p*-sulphonyloxy-group its behaviour is exactly similar to that of other known examples of 1-toluene-*p*-sulphonyl ketose derivatives. Other arguments in favour of (XIX) are the stability of sedoheptulosan to alkali and the fact that the dibasic acid obtained by bromine oxidation of the dialdehyde resulting from reaction with periodate is highly resistant to acid hydrolysis. The behaviour here runs parallel with that of levoglucosan (the 1 : 6-anhydride of D-glucose) and is readily understood in view of the structure of the dibasic acid which is in fact a derivative of 1 : 3-dioxolan. This brief account of sedoheptulosan serves to illustrate the ingenuity of method and argument which Hudson and his colleagues brought to bear on this complex and difficult field, but it must be remembered that this is one substance only of the many studied by them in the course of the past ten years.

Cyclic acetals and anhydro-sugars have recently acquired a new importance in carbohydrate chemistry. Their detailed structures are becoming known and the substances themselves are being used as starting materials in synthetic work. The simplicity and elegance of the methods of investigation which have been developed and the unambiguous nature of the conclusions are such that this whole chapter of work from Hudson's laboratory is likely to be regarded as a classic example of organic chemistry at its best.

While preparing this tribute to the memory of C. S. Hudson I have been privileged to have conversations with many of his friends and colleagues who joined with me in holding him in high regard as both a great man and a great chemist. To all those I express my thanks. I am particularly indebted to Professor C. B. Purves and Dr. Nelson K. Richtmyer for their kind co-operation in discussions, in the loan of manuscripts and figures, and in giving much friendly assistance in the preparation of this lecture.

OBITUARY NOTICES.

HAROLD GOVETT COLMAN.

1866—1954.

HAROLD COLMAN was born at Peterborough on February 5th, 1866. He was educated at Bishop's Stortford College and under Sir Henry Roscoe at Manchester. He became a Fellow of the Society and took his B.Sc. in 1887, followed by D.Sc. in 1908.

He became associated with W. H. Perkin, jun., in work upon the formation of closed carbon chains and in particular upon the derivatives of *cyclo*butane and *cyclo*pentane (*Trans.*, 1887, 228; 1888, 185) and upon 4-oxopentan-1-ol and 5-oxohexan-1-ol (*Trans.*, 1889, 352).

Colman became an assistant to Sir Henry Roscoe and was part editor of Roscoe and Schorlemmer's " Treatise " but his work in this country was interrupted by visits to Strasbourg University in 1885–86 and to Würzburg where he took his Ph.D. At Würzburg he worked, at the suggestion of Emil Fischer, upon the derivatives of methylindole (*Trans.*, 1889, 1).

In 1891, Dr. Colman was appointed to the teaching staff at Birmingham but in the following year, under the influence of Joseph Chamberlain, he gave up academic work in order to enter the City of Birmingham Gas Department as Chief Chemist. This proved to be an important step not only for Colman but for the gas industry. Although he relinquished this post in 1903 in order to devote his energy to consulting work he retained close contact with the industry throughout the remainder of his long life. At Birmingham Colman created an appreciation of the importance of chemistry in gas manufacture which long continued to act as a stimulus to the rest of the industry and particularly to the larger units of it. The present status of chemistry in coal carbonisation dates in no small degree from his example and enthusiasm at the close of the last century.

Colman was elected a member of the Institution of Gas Engineers in 1894 and a member of their Council in 1902—an unusual distinction for a chemist at that time. Although he published relatively few formal papers he took an active part in many technical discussions. His services were recognised by election to honorary membership in 1942.

While at Birmingham he published with J. F. Smith a paper on the Estimation of Naphthalene in Coal Gas based upon the use of picric acid (*J. Soc. Chem. Ind.*, 1900, **19**, 128) and later gave the results of his long experience (*Gas J.*, 1918, **144**, 231). He also acquired a specialised knowledge of the occurrence and behaviour of cyanogen compounds in the products of coal carbonisation. During the First World War he made outstanding contributions to the control of toluene recovery in coal-carbonising and tar-distilling works. With E. W. Yeoman he published papers on the Determination of Benzene, Toluene, etc., in Coal Tar (*J. Soc. Chem. Ind.*, 1919, **38**, 57T) and the Determination of Aromatic Hydrocarbons in Petrol (*ibid.*, p. 82T).

He was on the Council of the Chemical Society from 1912 to 1915. He was also a member of Council, an Examiner and, later, Vice-President of the Institute of Chemistry.

In a busy life Harold Colman found relaxation in Continental travel and as a woodworker. He is remembered with affection by his former colleagues because of his readiness at all times to help his juniors in every way. In later years he was seriously handicapped by loss of hearing but still retained that cheerfulness combined with charming modesty which was so characteristic. He died at New Malden on February 20th, 1954, and is survived by his wife and daughter.

H. HOLLINGS.

PIERRE JOLIBOIS.

1884—1954.

La chimie française a vu disparaître avec un infini regret l'un de ses plus distingués représentants dont la vie scientifique se déroula dans la plus parfaite harmonie. Il prit cependant une part très active aux manifestations collectives et fut même le créateur de certains rassemblements comme le Comité national de la Chimie, organisme de liaison entre la science et l'industrie, de représentation de notre pays à l'Union internationale de Chimie pure et appliquée.

Né dans une famille de magistrats le 23 Mai 1884, il fréquente le lycée Louis le Grand, puis il est élève à l'Ecole polytechnique de 1903 à 1905. Son service militaire effectué dans l'Artillerie Coloniale, il se consacre à la recherche de 1907 jusqu'à la première guerre mondiale sous la direction des Professeurs Lebeau et Le Chatelier, stage au cours duquel il soutint avec succès ses thèses de doctorat ès sciences (1910).

Dès l'abord ses travaux sont marqués d'une telle originalité qu'il est classé par Henry Le Chatelier parmi les esprits inventifs, capables d'accroître la connaissance en chimie.

Trois sujets le préoccuperont durant son séjour à la Faculté des Sciences : l'allotropie du phosphore, les phosphures, les organomagnésiens mixtes. Malgré la diversité de ces questions, un souci constant le guidera dès cette époque et le poursuivra d'ailleurs tout au long de sa carrière : l'introduction des méthodes de la physique expérimentale à la résolution de problèmes chimiques. Il frappe ainsi d'une sorte de sceau indélébile les qualités de son œuvre au laboratoire : propreté et minutie, élégance et esthétique.

Ainsi par des mesures de propriétés physiques pertinemment choisies (densité, tension de vapeur, chaleurs de transformation en cours de chauffage) et susceptibles de montrer les variations les plus nettes lors du passage d'une variété à une autre, il ramène à trois le nombre des variétés allotropiques du phosphore : le phosphore blanc, le phosphore rouge et celui qu'il obtient en chauffant ce dernier à 280° avec de l'iode comme catalyseur et qu'il désigne sous le nom de phosphore pyromorphique. A cette occasion il s'occupe également de l'allotropie de l'arsenic et il fixe au voisinage de 850° le point de fusion de cet élément.

Il en est de même pour les différents alliages de la famille des phosphures et siliciures où il met en œuvre l'analyse thermique et la métallographie microscopique, techniques récemment apparues à l'époque. Avec son premier maître le Professeur P. Lebeau, il met en évidence SiPd, isolable, et $SiPd_2$. Il rénove ensuite la préparation du P_2Zn_3 et admet l'existence de P_2Zn. Il isole deux phosphures d'étain : P_3Sn_4 et P_3Sn, ce dernier très oxydable ayant des propriétés pyrogènes semblables à celle du ferrocérium. Il réussit à séparer P_2Ni_5 et à obtenir par une voie détournée les alliages riches en phosphore : P_2Ni et P_3Ni. Il démontre en outre l'existence des arséniures As_3Sn_4 et AsSn.

P. Jolibois rapporte que son incursion dans l'étude des organométalliques (1912) est une application de la technique du vide qui s'avérait fructueuse dans d'autres domaines. En fait il présente des arguments en faveur de la constitution X_2Mg,R_2Mg * des composés organomagnésiens mixtes de V. Grignard, il indique le principe de leur dosage par iodométrie et il découvre l'hydrure H_2Mg ainsi que le carbure CMg_2, celui-ci lié à une molécule de I_2Mg sous forme d'une combinaison jaune, insoluble dans l'oxyde d'éthyle.

Mobilisé en 1914 comme lieutenant de réserve d'Artillerie et nommé capitaine au début de 1915, il commande jusqu'en 1916 une batterie de 75 prenant part aux batailles du Grand Couronné, du Bois-le-Prêtre et de Verdun. Décoré de la Croix de Guerre, il dirige alors le laboratoire de la Poudrerie nationale de Bassens spécialisé dans la fabrication de l'acide picrique qu'il perfectionne rapidement ; il trouve un nouvel explosif, un dinitrobromophénol, relevé des eaux résiduaires de cette fabrication et qui sera adopté pour les tirs de réglage, en raison de la visibilité remarquable du nuage formé par l'explosion. En 1918, il est Chef du Service des bombes d'avion à l'Aéronautique militaire : sa perspicacité a tôt fait de découvrir la cause des explosions prématurées survenant trop fréquemment dans la manipulation de tels engins et d'empêcher qu'elles se produisent. A ces titres militaires de la première guerre mondiale, ajoutons que dégagé de toute obligation militaire en 1939, il reprend cependant du service au Ministère de l'Armement.

A la fin des hostilités (1919), P. Jolibois est chargé de mission au contrôle de la Badische Anilin und Soda Fabrik. Il reviendra trente ans plus tard à Ludwigshafen pour présider de

* En 1950, il publie une revue sur l'évolution des théories relatives à cette constitution : la question de structure simple ou double reste ouverte (*Bull. Soc. chim.*, 1950, 919).

1948 à 1953 le Conseil de Gérance de l'I.G. en dissolution, où son rôle à la fois ferme et conciliant est très apprécié. A l'expiration du mandat de ce Conseil, il reçoit les félicitations du Gouvernement. Aussi clairvoyant administrateur qu'habile expérimentateur, il nous lègue des liaisons et des accords dont étudiants, chercheurs ou industriels peuvent désormais bénéficier.

Rendu à la vie civile, la chaire de chimie générale de l'Ecole Nationale Supérieure des Mines lui est confiée en 1921. Avec l'appui d'une Direction compréhensive, il en fait un centre remarquable de recherches physico-chimiques, encore en pleine activité au moment de sa mort survenue à quelques mois de sa retraite.

Dans ce cadre progressivement amélioré se développent les études sur les phénomènes de précipitation, sur le plâtre, sur l'enregistrement photographique des réactions, ainsi que des contributions considérables dans les domaines de l'électrochimie et de la spectrochimie. Les exemples cités ci-après n'en donnent qu'un pâle aperçu.

Sa technique de précipitation est basée sur l'emploi d'un appareil réalisant en un temps très bref un mélange homogène de liquides. Grâce à ce dispositif aussi simple qu'ingénieux, lui-même et ses élèves distinguent aisément les composés définis des mélanges. Ainsi sont étudiées systématiquement les précipitations des phosphates de calcium, des sels mercuriques par l'hydrogène sulfuré, du nitrate d'uranyle par la soude. La méthode sert également à observer le fractionnement au cours de la précipitation, à déterminer les conditions de formation des sels basiques comme aussi l'état de précipités instables qui se transforment rapidement avec le temps, tel que l'iodure mercurique jaune (magnifique expérience de cours).

Les recherches sur le sulfate de calcium aboutissent à des conclusions pratiques, notamment à la construction d'un prisomètre à l'aide duquel on détermine une caractéristique de chaque sorte de plâtre : la variation de la température en fonction du temps d'un mélange en proportions connues d'eau et du plâtre considéré. D'autre part la connaissance exacte du rôle joué par chacun des composants du plâtre permet d'obtenir un matériau de qualités variables au gré du fabricant (vitesse de prise et dureté après durcissement) en associant des quantités convenables de gypse, de semi-hydrate et de surcuit.

En électrochimie, P. Jolibois étudie d'abord les actions engendrées par l'étincelle dans les gaz raréfiés. Il choisit la décomposition de l'anhydride carbonique bien connue du point de vue de la thermodynamique et il observe son évolution dans un tube à décharges en examinant tour à tour l'influence des électrodes, du voltage, de l'intensité, de la pression, des différentes régions de l'étincelle. Dans chaque cas il mesure le rendement énergétique et le degré d'avancement de la réaction ; il fait alors d'intéressants rapprochements avec les dissociations strictement pyrogénées.

Il constate en outre que le voisinage d'une cathode subissant une pulvérisation électrique est le siège de phénomènes catalytiques intenses. D'où la découverte d'une préparation d'ammoniac par synthèse directe à température ordinaire et avec une concentration qu'aucun procédé n'a encore réalisé à ces bases pressions.

Les recherches se poursuivent alors sur l'étincelle positive jaillissant à la surface d'une solution conductrice. Il en sépare plusieurs phénomènes lumineux distincts, examine les facteurs dont ils dépendent. Il réussit à mettre au point un procédé assez général d'analyse quantitative par spectrographie.

L'électrolyse à l'aide d'une étincelle négative lui ayant fourni un dépôt d'oxyde obéissant à la loi de Faraday, il étend ces résultats à l'électrolyse ordinaire en l'effectuant avec des électrodes formées d'eau distillée, et il en déduit des vues originales sur le phénomène élémentaire de l'électrolyse.

En marge de cette œuvre si dense, Pierre Jolibois apporte un concours empressé et généreux aux groupements scientifiques ou professionnels (Société Chimique de France, Société de Chimie Physique, Maison de la Chimie, Palais de la Découverte, Centre National de la Recherche Scientifique, Union internationale de Chimie pure et appliquée etc. . . .) comme à certains organismes de sécurité de la Nation (Comités d'action scientifique : des Poudres, de la Défense nationale). Il préside bon nombre d'entre eux avec une aménité et une distinction naturelles, de juste renommée. Aussi ses élèves, ses collaborateurs et ses amis se réjouissent-ils particulièrement de le voir entrer à l'Institut en 1944 dans la Section de Chimie de l'Académie des Sciences et lorsqu'il reçoit en 1951 la cravate de Commandeur de la Légion d'Honneur.

Ils conservent le pieux souvenir d'un homme accueillant, spirituel et cultivé, ironisant parfois mais avec bienveillance. Ils évoquent avec émotion sa bonté, sa générosité, son inébranlable fidélité dans l'amitié. Ils s'inclinent encore devant le stoïcisme qu'il montra lors de la cruelle épreuve de sa vie : la mort tragique d'un fils de vingt ans qui embrassait la même carrière.

Pierre Jolibois avait tant d'attrait pour la Science expérimentale qu'il avait fait construire un laboratoire dans sa propriété des bords de la Sarthe. On songe avec mélancolie que ses murs ne verront plus jamais leur maître : il aurait laissé encore moins de pages blanches dans le livre fondamental de la Chimie.

R. DELABY.

NICHOLAS DIMITRIVICH ZELINSKY.

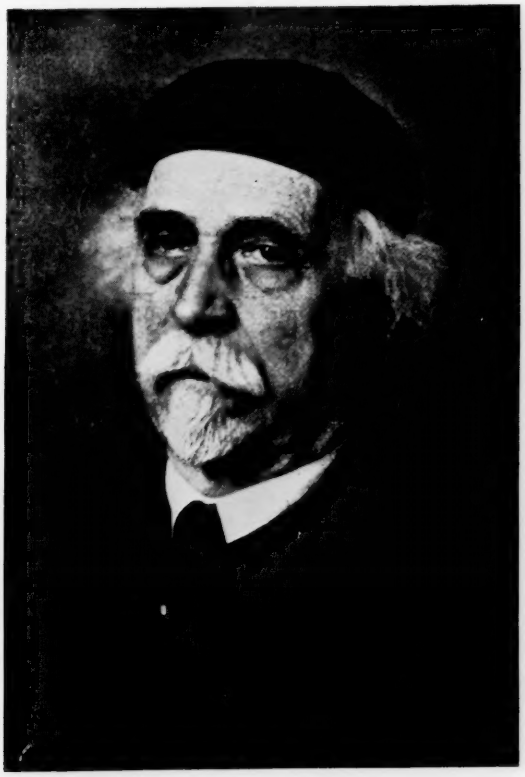
1861—1952.

NICHOLAS DIMITRIVICH ZELINSKY was born on February 6th, 1861, in Tiraspol in the Russian Province of Kherson. He received his school training in Tiraspol and in Odessa where he afterwards went to the University of Novorossisk. Later he studied in Leipzig and in Göttingen, working there in the laboratory of Victor Meyer. In 1888 Zelinsky obtained his master's degree and was appointed a lecturer at his old University of Novorossisk where in the next 3 years he presented two theses, one in 1889 dealing with " Isomerisation in the Thiophene Series " for his master's degree and the other in 1891 entitled " Research on the Phenomenon of Stereoisomerism in Saturated Carbon Compounds " for his doctorate. In 1893 he was appointed adjunct professor at the University of Moscow where, with the exception of the period 1911—17, he was to spend the remainder of his life. There Zelinsky took charge of the analytical chemistry laboratory and shared with Markovnikov, until the latter's death in 1904, the Department of Organic Chemistry. Zelinsky gave the lectures on organic chemistry, which were profusely illustrated by experiments and a very large collection of specimens and were outstanding because of their clarity and simplicity. The organic chemistry laboratory, built in 1885—87 by Markovnikov and situated in a low and damp cellar, was not large enough to hold all the students who wished to work with Zelinsky. In spite of such unfavourable surroundings the young Professor was able to impart his enthusiasm to those working with him, who gave little thought to Sundays and holidays. At times they indulged in choral singing in the laboratory for which Zelinsky received a reprimand from the Ministry of Education. In 1902, however, Zelinsky was provided with a new annexe which still to-day houses the teaching and research laboratories of the Department of Organic Chemistry. During this time Zelinsky spent a considerable time on social work and teaching outside the University. He organised a chair of Organic Chemistry in the Moscow Course of Higher Education for Women and also the Central Laboratory of the Ministry of Finance in Moscow which later became the Institute of Pure Chemical Reagents.

In 1911 the entire administration of Moscow University was dismissed by order of the Ministry of Education and, in token of protest, the teaching staff, including Zelinsky, resigned. Zelinsky went to St. Petersburg where he directed the laboratory of the Ministry of Finances and taught at the Polytechnic Institute. Only in 1917, after the revolution, was he able to return to Moscow where he resumed his teaching with enthusiasm and energy, combining it after 1934 with the direction of the Institute of Organic Chemistry of the U.S.S.R. Academy of Sciences. At the time of his 90th birthday, Zelinsky held the chair of the chemistry of petroleum in the Faculty of Chemistry of the Moscow State University, was in charge of a section of the Organic Chemistry Institute of the Academy of Sciences, and was President of the Moscow Society of Naturalists. He died on July 31st, 1952, at the age of 91.

During his academic life, Zelinsky published over 500 papers with his many students who include some of the foremost organic chemists in Russia to-day.

Although Zelinsky's major contributions were in the field of hydrocarbon chemistry, from the beginning of his scientific career he was interested in biochemistry, particularly in the chemistry of amino-acids and proteins. His first publication entitled " On the Addition Products of Methylamine and β-Methylglycidic Acid " appeared in the Journal of the Russian Chemical Society in 1884 while he was still a student in Odessa working under Professor Melikov. His interest in this field continued throughout his life and the work was described in a number of papers published with his students. He prepared and studied a large number of amino-acids using the ketone cyanohydrin synthesis which he had developed (1906—1908) and obtained for the first time several important amino-hydroxy-acids. Following E. Fischer's work he investigated the hydrolysis of proteins with dilute hydrochloric acid in an autoclave at 180°, separating the product by means of organic solvents. An account of this work, published with V. S. Sadikov in 1923 and covering ten years' research, demonstrated the important part



N. Zelinsky

To face p. 4062.

played by diketopiperazines in building up the complex protein molecule. For their research on protein chemistry, Zelinsky and Gavrilov were awarded a Stalin prize in 1948.

Zelinsky's chief interest was, however, in hydrocarbons and their reactions, and to this field he contributed much. He synthesised a large number of hydrocarbons, in particular *cyclo*paraffins, which brought him into contact with both terpene and petroleum chemistry. In 1895 he prepared the first synthetic naphthene, 1 : 3-dimethyl*cyclo*hexane, from $\alpha\alpha'$-dimethylpimelic acid by cyclisation and reduction of the resultant ketone to the hydrocarbon and showed its close similarity to the "octonaphthene" separated from Caucasian petroleum by Markovnikov. Employing a similar procedure he prepared a number of other *cyclo*hexanes and *cyclo*pentanes. In his synthesis of hydrocarbons, Zelinsky made considerable use of the organometallic compounds of magnesium and zinc and obtained many unusual compounds including *cyclo*propane, *cyclo*butane, *cyclo*heptane, *cyclo*octane, and *cyclo*nonane, being the first to synthesise the last. Besides saturated *cyclo*paraffins he prepared *cyclo*alkenes and *cyclo*alkadienes, often by unusual methods. *cyclo*Pentadiene, normally prepared by depolymerising the dimer, was synthesised by Zelinsky from *cyclo*pentene which he converted into 1 : 2-dibromo*cyclo*pentene and then dehydrobrominated. *cyclo*Hexadiene was obtained by a novel route involving treatment of *cyclo*hexane with selenious acid and acetic anhydride to give *cyclo*hexenyl acetate and converting this into the diene with potassium hydrogen sulphate. Zelinsky devoted considerable time to the synthesis of difficultly accessible ring systems including bicyclic and *spiro*-hydrocarbons. During this work he observed and investigated several intra-annular rearrangements similar to those which occur with terpene hydrocarbons.

Zelinsky's investigations of the conversion reactions of hydrocarbons in the presence of catalysts were outstanding and eventually led to establishment of a school of contact catalysis under his leadership. In 1911, while searching for a catalyst which would enable the dehydrogenation of *cyclo*hexane to be carried out at temperatures low enough to avoid pyrolysis, *i.e.*, not exceeding 300—310°, Zelinsky discovered that platinum and palladium black were both capable of converting *cyclo*hexane into benzene at 300° and, furthermore, were equally effective in hydrogenating benzene to *cyclo*hexane at 110° : in the presence of these catalysts the reaction was, in fact, reversible. He later showed that the metal could be deposited on asbestos or activated charcoal and that the supported catalysts so prepared were particularly active and stable. Under the conditions suitable for dehydrogenating *cyclo*hexane, *cyclo*pentane and *cyclo*heptane were unaffected and *cyclo*octane behaved abnormally to give methyl*cyclo*heptane and bi*cyclo*octane. Subsequently Zelinsky found that nickel supported on alumina was an equally effective catalyst in dehydrogenating hydrocarbons with a *cyclo*hexane ring, which was surprising since Sabatier had earlier found that pure nickel by itself brought about complete decomposition of *cyclo*hexane. An exhaustive study of the Zelinsky nickel–alumina catalyst was undertaken by his pupil A. M. Rubenstein who demonstrated that, with few exceptions, all hydrocarbons containing *cyclo*hexane rings readily underwent dehydrogenation to the corresponding benzene derivatives. A noteworthy exception was *cyclo*hexane itself which yielded under similar conditions a mixture containing toluene, xylene, and dimethyl*cyclo*hexane, the formation of which was regarded by Zelinsky and Shuikin as indicative of the participation of free radicals in the reaction. The few hydrocarbons containing the *cyclo*hexane ring which were not dehydrogenated included norbornylene (3 : 3 : 1-*bicyclo*heptane) and 1 : 1-dimethyl-*cyclo*hexane. The former was completely unaffected and this was attributed to the presence of two fused *cyclo*pentane rings in its structure. Some aromatisation of 1 : 1-dimethyl*cyclo*hexane occurred, involving the elimination of methane as well as of hydrogen. The selective dehydrogenation of *cyclo*hexane derivatives over a platinum catalyst to-day forms the basis of a method widely used for the detection and determination of the *cyclo*hexane ring. The recently developed "Platforming" process, extensively employed in the petroleum industry for the large-scale production of aromatic hydrocarbons from petroleum fractions, which uses a platinum catalyst, can be considered an outcome of Zelinsky's discovery of the dehydrogenating properties of platinum and palladium.

In their investigation on the dehydrogenation of *cyclo*hexanes present in gasoline fractions, Zelinsky and Shuikin observed that the yield of aromatic hydrocarbons was often greater than would be expected from the amounts of *cyclo*hexanes present and concluded that other hydrocarbons were also undergoing aromatisation. Further investigation by Zelinsky and his colleagues and by Moldavsky and Kamushev led to the discovery that paraffins undergo cyclisation in the presence of chromia–alumina to give aromatic hydrocarbons.

This reaction received considerable prominence in the years immediately preceding the last war (1936—1939) since it appeared to offer an excellent method of producing aromatic

hydrocarbons from petroleum. However, owing principally to loss of activity caused by decomposition of *cyclo*pentanes giving excessive carbon deposits, the process was eventually modified so that mainly *cyclo*hexane dehydrogenation was involved. Since this could be done at lower temperatures, pyrolysis of the *cyclo*pentanes was avoided.

While investigating the dehydrogenation of dimethyl tetrahydrophthalate, Zelinsky and Glinka found that in contact with platinum black at room temperatures it was converted into a mixture of the hexahydrophthalate and phthalate. This form of disproportionation was shown by Zelinsky and Pavlov to take place also with *cyclo*hexene, three molecules of *cyclo*hexene giving two molecules of *cyclo*hexane and one of benzene. Unlike the *cyclo*hexane–benzene dehydrogenation–hydrogenation this reaction was completely irreversible. A favourite lecture demonstration of Zelinsky's was to add *cyclo*hexadiene cooled to $-20°$ to palladium black and show that the heat evolved in the reaction was sufficient to make the benzene and *cyclo*hexane formed boil vigorously.

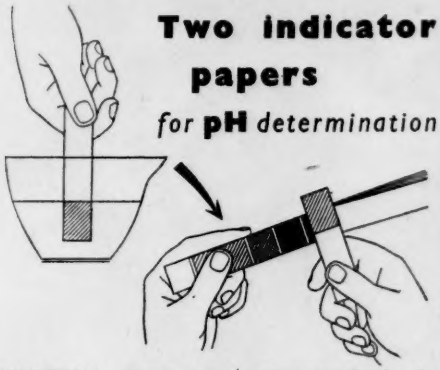
Irreversible disproportionation of this type only occurs with *cyclo*hexene and *cyclo*hexadiene derivatives capable of producing an aromatic ring, 1 : 3 : 3-trimethyl*cyclo*hexene, for example, remaining unchanged. Molecules such as methylene*cyclo*hexane or vinyl*cyclo*hexane react, however many carbon atoms are interposed between the double bond and the ring. This behaviour was attributed to the migration of the double bond into the ring. That this explanation was correct was demonstrated by Zelinsky and (Miss) R. Ya Lavina by placing a quaternary carbon atom in the side chain as a barrier between the double bond and the *cyclo*hexane ring : no reaction then took place.

The isomerisation of *cyclo*paraffins involving change in ring size was first observed by Zelinsky in 1905, when, on treatment of ethyl*cyclo*pentane with aluminium bromide and bromine, pentabromotoluene was formed—a reaction which could have occurred only through the intermediate formation of methyl*cyclo*hexane. Other instances of the isomerisation of *cyclo*pentanes by aluminium halide catalysts were also investigated. In 1898 he devised an original method for estimating petroleum fractions based upon the treatment of the latter, freed from aromatic hydrocarbons by means of sulphuric acid, with a complex of acetyl chloride and aluminium chloride which converted the naphthenes into ketones while leaving the paraffins unattacked. This provided a useful method for separating the two types of hydrocarbons. At about the same time Zelinsky became actively concerned in the production of aromatic hydrocarbons from petroleum by pyrolysis and a plant was set up near Kineshma with his assistance to make benzene in this way. Some years later, during the 1914—1918 war, several such plants were erected and operated in the Caucasus to provide much needed toluene for explosives. The relatively low yield obtained by pyrolysis led Zelinsky to investigate alternative methods for producing aromatics. As early as 1913 by dehydrogenating the 100—104° petroleum fraction containing the methyl*cyclo*hexane he had obtained a product with a toluene content of 50%, thus forestalling the modern dehydrogenation processes. With Kasansky he investigated the conversion of acetylene into benzene by passage over activated charcoal at 600° and obtained a 74% yield of liquid product of which 35% was benzene.

Apart from his investigations into the composition of petroleum Zelinsky was particularly interested in its origin. He examined sapropelite found on the edge of Lake Balkhash as a possible source of natural petroleum, showing that on dry distillation, in addition to gas and coke, as much as 63% of tar could be obtained which in turn yielded gasoline, kerosene, and paraffins on redistillation. As far back as 1891 Zelinsky was a member of an expedition which investigated the waters of the Black Sea and proved the bacterial origin of the hydrogen sulphide formed in its depths, a mission which no doubt prompted his interest in problems related to the formation oil under similar conditions.

In recognition of Zelinsky's achievements in the field of organic chemistry he was in 1940, on the occasion of the 180th anniversary of Moscow University, awarded the highest honour of the U.S.S.R., the order of Lenin. On two later occasions he was again awarded this honour, in 1945 at the 220th anniversary of the Academy of Sciences and again in 1946, on his 85th birthday. On three occasions he was also awarded Stalin prizes, in 1942 for his work in organic chemistry, in 1946 with Shuikin and Novikov, and in 1948 with Gavrilov for research on the chemistry of proteins. Besides these he received a number of other honours and was in 1943 elected an honorary Fellow of the Chemical Society.

S. F. Birch.



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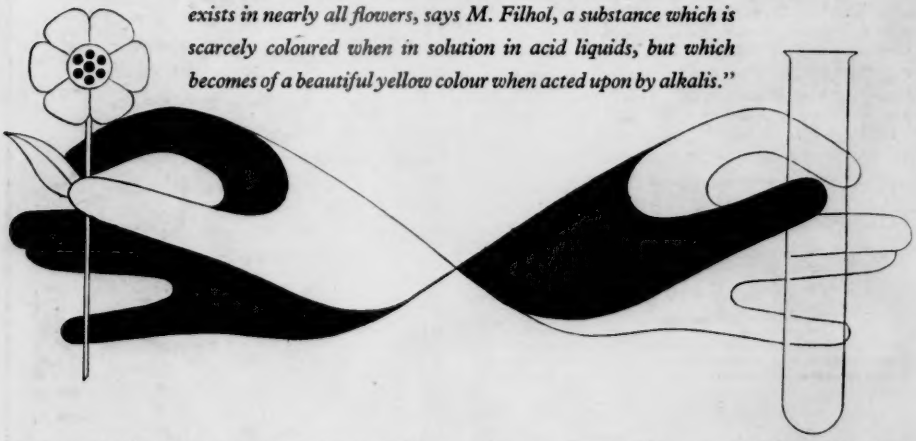

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